AMERICAN JOURNAL
OF
OBSTETRICS AND GYNECOLOGY

ADVISORY EDITORIAL BOARD

FRED L. ADAIR
BROOKE M. ANSPACH
JAMES R. BLOSS
LUCIUS E. BURCH
WALTER W. CHIPMAN
WILLARD R. COOKE
HARRY S. CROSSEN
THOMAS S. CULLEN
ARTHUR H. CURTIS
WILLIAM C. DANFORTH
WALTER T. DANNREUTHER
CARL H. DAVIS
ROBERT L. DICKINSON
PALMER FINDLEY
C. FREDERIC FLUHMANN
ROBERT T. FRANK
WILLIAM P. HEALY
F. C. IRVING
JENNINGS C. LITZENBERG
JAMES C. MASSON
HARVEY B. MATTHEWS
JAMES R. MCCORD
NORMAN F. MILLER
EMIL NOVAK
EVERETT D. PLASS
ISIDOR C. RUBIN
JOHN A. SAMPSON
OTTO H. SCHWARZ
H. J. STANDER
PAUL TITUS
HERBERT F. TRAUT
NORRIS W. VAUX
GEORGE GRAY WARD
BENJAMIN P. WATSON
PHILIP F. WILLIAMS
KARL M. WILSON

OFFICIAL ORGAN

THE AMERICAN GYNECOLOGICAL SOCIETY; THE AMERICAN ASSOCIATION OF OBSTETRICIANS, GYNECOLOGISTS, AND ABDOMINAL SURGEONS; NEW YORK OBSTETRICAL SOCIETY; OBSTETRICAL SOCIETY OF PHILADELPHIA; BROOKLYN GYNECOLOGICAL SOCIETY; ST. LOUIS GYNECOLOGICAL SOCIETY; NEW ORLEANS GYNECOLOGICAL AND OBSTETRICAL SOCIETY; BALTIMORE OBSTETRICAL AND GYNECOLOGICAL SOCIETY; CHICAGO GYNECOLOGICAL SOCIETY; CINCINNATI OBSTETRIC SOCIETY; CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS; AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY; WASHINGTON GYNECOLOGICAL SOCIETY; PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY; OBSTETRICAL SOCIETY OF BOSTON; LOUISVILLE OBSTETRICAL AND GYNECOLOGICAL SOCIETY; SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS; SEATTLE GYNECOLOGICAL SOCIETY; SOCIETY OF OBSTETRICIANS AND GYNECOLOGISTS OF CANADA; ALABAMA ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS; AKRON OBSTETRICAL AND GYNECOLOGICAL SOCIETY; KANSAS CITY OBSTETRICAL AND GYNECOLOGICAL SOCIETY; CENTRAL NEW YORK ASSOCIATION OF GYNECOLOGISTS AND OBSTETRICIANS

EDITOR
GEORGE W. KOSMAK

ASSOCIATE EDITORS
HOWARD C. TAYLOR, JR. . . . WILLIAM J. DIECKMANN

VOLUME 54
JULY—DECEMBER, 1947

ST. LOUIS
THE C. V. MOSBY COMPANY
1947

UNIVERSITY OF CALIFORNIA
LIBRARY
COLLEGE OF AGRICULTURE
DAVIS

Copyright, 1947, by The C. V. Mosby Company

(All Rights Reserved)

Printed in the
United States of America

Press of
The C. V. Mosby Company
St. Louis

American Journal of Obstetrics and Gynecology

VOL. 54 JULY, 1947 No. 1

Original Communications

ON THE PROPHYLAXIS OF HEMOLYTIC DISEASE OF THE NEWBORN

DONALD H. KARIHER, M.D., ROCHESTER, N. Y., WITH THE TECHNICAL ASSISTANCE OF DOROTHY I. MILLER

(From the Department of Obstetrics and Gynecology the University of Rochester School of Medicine and Dentistry)

IT WOULD seem that it is now possible to diagnose hemolytic disease of the newborn in the as yet unborn infant in nearly all cases.[1] This can be done by routinely testing the sera of all Rh-negative mothers during their pregnancies for the presence of one or more of the Rh antibodies, and obtaining titers of the amount of antibody if any is present.[2] Being aware before delivery of the fact that an infant with hemolytic disease of the newborn is to be delivered, one can make preparations for the proper treatment of the infant following its birth. This preparation and treatment resolves itself into having available Rh-negative blood of the proper group, and transfusing the infant immediately at birth or as soon thereafter as seems justified by the condition of the baby, and particularly by the red blood cell and hemoglobin levels. Repeated blood transfusions are nearly always necessary.

By this means the mortality rate in liveborn infants suffering from hemolytic disease of the newborn has been reduced to between 9 per cent[3] and 33 per cent.[4] Obviously, this form of treatment of the infant, helpful as it has been, is far from being satisfactory. Aside from failing in still a large percentage of liveborn infants, it of course is useless if the infant is stillborn or if the patient aborts the pregnancy early during its course. The ideal treatment, which would actually be prophylactic in nature, is the treatment of the mother during her pregnancy. This treatment could be directed at one of three objectives: (1) the prevention, by some chemical means, of the antigen-antibody reaction from going to completion. This, of course, is the essential reaction in the production of hemolytic disease of the newborn; (2) the absorption of the antibody as soon as it is formed by means of Rh haptene injections; or (3) inhibition of antibody by some immunologic means.

NOTE: The Editors accept no responsibility for views and statements of authors as published in their "Original Communications."

65159

Wiener has suggested this[5] objective in his theory of "competition of antigens." He believes that if two or more antigens of unequal potency are given an individual, that individual will produce an antibody against the stronger antigen, and produce little, if any, against the weaker antigen. He believes that since the Rh antigen is a relatively weak one, pertussis and typhoid vaccines given at intervals during the course of a patient's pregnancy might inhibit or prevent the formation by that patient of the Rh antibodies.

Following this line of reasoning we gave one patient weekly injections of A and B specific substances (Eli Lilly and Co.), which are relatively strong antigens during the last six months of pregnancy without having any effect on the course of her Rh-antibody production, and with the result that she delivered an infant which died from hemolytic disease of the newborn on its fourth day of life.

To the writer's knowledge, the Rh haptene has not been obtained in any form which would make it useful clinically. Thus, the second of the above objectives is probably not attainable at present.

The purpose of this communication is to present three cases which have been treated with the first objective in mind, that is, the prevention by some chemical means of the antigen-antibody reaction going on to completion. In all three cases the patients have previously delivered one or more infants which have died of hemolytic disease of the newborn. In two of these cases the patients have, following treatment, delivered infants which appeared normal at birth and remained so during the period of observation. In the third case the infant had hemolytic disease of the newborn, but survived following repeated transfusions. The treatment consisted of weekly intramuscular injections of 2.0 c.c. of ethylene disulfonate (Allergosil Brand)* during the last three, four, and six months of the pregnancies, respectively. In two of the cases the hemolytic disease in the previous pregnancies was due to an Rh incompatibility, while in the other case it was due to an O-A incompatibility, the mother being group O and the infant group A. Because of the small number of cases, this report is being published with the hope that others will attempt to corroborate the findings presented here. The relative paucity of suitable material would make the collection of a large series of cases by any single clinic a very prolonged experiment. This report is not being published as a cure for hemolytic disease of the newborn.

Theory

Knowing that the production of hemolytic disease of the newborn in affected infants is essentially an antigen-antibody reaction, the idea suggests itself that if one portion of the reaction is eliminated, the reaction then cannot go to completion. Obviously, the antigen on the fetal red cells cannot be eliminated. Some process then of preventing the production of antibody, or of destroying it as fast as it is produced must be achieved. We have observed[6] that out of several thousand tests of the sera of pregnant Rh-negative women for the agglutinating and conglutinating antibodies, in only two instances have

*This material was very generously supplied for experimental work by the Spicer-Gerhart Company, Pasadena, California.

we found one or more of the Rh antibodies of any degree in the mother without having that mother later deliver an infant with hemolytic disease of the newborn. Likewise, since the institution of routinely testing the sera of all pregnant women for the presence or absence of both agglutinating and conglutinating antibodies, no instances have been found where a diseased infant was born from a mother who had not previously demonstrated the presence of one or more of the Rh antibodies in her serum, except in those instances where the disease was due to some blood incompatibility other than Rh.[4] We have also observed, as have others, that the level of Rh antibody titer in the mother bears no correlation with the severity of the disease in the infant. It would seem reasonable, however, in view of the above statements, that if the Rh antibody could be eliminated from the maternal circulation, the infant should be normal at birth and remain so.

To this end, a drug which has been used in allergic states was employed, mainly ethylene disulfonate (Allergosil Brand). Its use in allergic conditions was based on the conclusion of the British and Belgian observers; Evans, Bodman, and Maisin,[7] that in allergic states there is some abnormality of the cellular metabolism of carbohydrate, which in turn is due to the absence of a certain oxidation catalyst in the body. These workers also concluded that ethylene disulfonate would act as an oxidation catalyst and thus restore the cellular carbohydrate metabolism to normal, which in turn would alleviate the allergic manifestations. They present both case histories and animal experiments in support of their conclusions. They feel that a physiologic dilution of the drug is between $1:10^{-10}$ and $1:10^{-18}$, and used a dilution of $1:10^{-15}$ in their case studies and animal experiments. Fisk, Small, and Foord,[8] using ethylene disulfonate in an attempt to protect guinea pigs against anaphylactic shock, found that it did not produce a significant degree of protection. In fact, they found that distilled water alone produced approximately the same amount of protection.

In the present study, the dilution of the chemical was $1:10^{-15}$ in triple distilled water, as packaged by Spicer-Gerhart under the name ethylene disulfonate (Allergosil Brand). This great dilution means that each 2.0 c.c. injection (the dosage used) contains 0.000000000002 mg. of ethylene disulfonate. It would seem that this dilution is practically distilled water, and it may be that the results to be reported are due to the intramuscular injection of distilled water rather than to the infinitesmal amount of ethylene disulfonate in the solution. However, it is not within the scope of this paper to discuss the theoretical chemical reactions involved, but merely to report the results. Recently[9] the Council on Pharmacy and Chemistry of the American Medical Association has published a lengthy discussion of ethylene disulfonate (Allergosil Brand), and has found it not acceptable for inclusion in *New and Nonofficial Remedies*.

Experimental

In Rochester, New York, a plan has been in operation since Oct. 1, 1945, for carrying out routine Rh determinations on all pregnant women.[1] The sera of all Rh-negative patients are studied at intervals throughout the course of their pregnancies for the detection of one or more of the Rh antibodies. It was from this source that the three cases to be described in detail were chosen. They were chosen in each instance because of a history of hemolytic disease of the newborn in a previous pregnancy, proved by clinical and pathologic studies. These patients were in varying stages of their pregnancies when this study was started, and in each instance it was felt that another infant would be born with hemolytic disease. This was thought to be so, since in each instance the patient already carried a high titer of Rh (2 cases) or A (1 case) antibody in her serum. In each case 2.0 c.c. of ethylene disulfonate (Allergosil Brand)

in a dilution of $1:10^{-15}$ in triple distilled water was given intramuscularly at weekly intervals until labor was established. This meant that the first patient to deliver (case 1) received 12 injections, the second patient (case 2) received 10 injections and the third patient (case 3) 20 injections. Weekly samples of blood were withdrawn from the patient, and the serum so obtained was titered for the level of the particular antibody in question. Prior to titration, the sera were inactivated by placing them in an incubator at 56° C. for thirty to forty-five minutes. The titrations were carried out in 6 mm. tubes by the dilution method as described by Wiener,[10] using pipettes, and making very careful dilutions. When the agglutinating antibody titration was being carried out, saline was the suspending medium and diluent for the Rh-positive red blood cells. When the "conglutinating" antibody[11] titer was being studied, serum from a group AB individual was used as the suspending medium and diluent. Although new batches of saline were used frequently during the course of the study, the AB serum was a constant. The red blood cells used as test cells in the anti-Rh titrations were group O Rh positive and were always used fresh from the same individual. It was not found possible to obtain blood the red cells of which were used in the anti-A titrations from the same individual throughout the entire course of the period of observation with the result that in that particular study the red blood test cells was a variable. All tests were carried out by the same individual, who is a capable and experienced worker in this field. In many instances the titrations were checked.

In the anti-Rh titrations, the tubes were placed in a water bath at 42° C. for one hour, centrifuged at 500 r.p.m. for one minute and the sediment read both macroscopically and microscopically for agglutination. In the anti-A titrations, the tubes were allowed to stand at room temperature for one hour, centrifuged at 500 r.p.m. for one minute and the sediment read both macroscopically and microscopically for agglutination. Readings were recorded as ++++, +++, ++, + and ±. The last tube showing ± agglutination was established as the end point.

When labor was established the mothers were given vitamin K in the form of Synkamin,* 2.0 c.c. intravenously. At the time of delivery the cord was not clamped until pulsations had stopped. After the cord had been cut, blood was milked from the maternal end for later study. Heel puncture of the infant was carried out and capillary blood obtained for red blood cell, white blood cell, hemoglobin, icterus index and prothrombin determinations as well as for blood smears. Sections of placenta and cord were obtained for pathologic study.

The infants were observed closely during their hospital stay. During the first three or four days red blood cell and hemoglobin determinations were carried out every six hours. For the next two or three days these determinations were made twice daily, and following that once daily. Icterus index determinations were made at frequent intervals, otherwise the infants were handled as normal newborns.

The cord blood was made use of in an attempt to find Rh antibody in the fetal blood. This was tested for by both the ordinary test tube method using the serum, and by the method suggested by Carter and Loughrey[12] using the red cells. The saliva of the infant described in Case 2 was tested for the presence of A factor.

Case Reports

CASE 1.—Mrs. G. S., a 23-year-old para i, gravida iv. Wassermann reaction negative. The obstetric and transfusion histories are summarized in considerable detail as follows: In 1939 the patient was given five transfusions, the Rh type of which is unknown. She had a reaction to one of these transfusions. Her

*Parke, Davis and Company, Detroit, Mich.

first pregnancy terminated in 1943 with the delivery of a living 1,990 Gm. male infant which died the following day. Diagnosis prematurity. Rh unknown. Two more transfusions were given the patient at this time, the Rh unknown, but there was a reaction after the second transfusion.

In May, 1944, the first Rh test was done on the patient. She was found to be group A Rh negative and to have no Rh antibody in her serum (agglutinating test only). At the time of this test the patient was about four months pregnant, her expected date of confinement being Oct. 6, 1944. Her husband is group O Rh positive.

On Sept. 18, 1944, Rh blocking antibody (Wiener[13]) was found in the maternal serum. However, this was the first time the blocking antibody had been tested for; the agglutinating antibody was negative. On Sept. 21, 1944, this second pregnancy terminated by midforceps delivery of a living 3,800 Gm. male infant after a 34-hour labor. The infant required resuscitation. His skin had a lemon yellow tint; the conjunctivae were icteric, as was the cord; the scrotum was very edematous; the abdomen was very distended and the skin of the abdomen showed pitting edema. A large liver was readily percussed, but the exact edge could not be palpated because of abdominal distention. The spleen was not felt. Numerous petechial hemorrhages appeared on the body and face during the first hour of life.

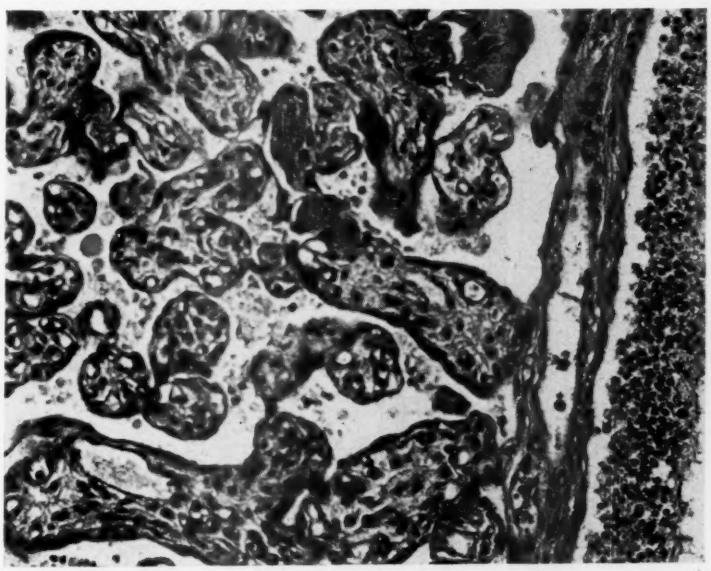


Fig. 1.—Photomicrograph of placenta from Case 1. Infant born 1944, died ten hours after birth from hemolytic disease of the newborn. Large vessel at top shows many nucleated red blood cells. The villi are thick, heavy, blunt. Stroma is heavy. (×210.)

Two hours after birth the infant was transfused with 70 c.c. of group A Rh-negative blood. Hemoglobin at the end of this transfusion was six grams. Eight hours after birth a transfusion of 50 c.c. group A Rh-negative blood was performed. Ten hours after birth the infant expired. Blood typing—group A, Rh positive.

Clinical diagnosis: Erythroblastosis fetalis.

Anatomic diagnosis following autopsy: Erythroblastosis fetalis.

Placenta: weight 860 grams. Ratio of placental weight to that of fetus 1:4.4. Cotyledons grossly were large, very smooth, pale pink color.

Pathologist's diagnosis: erythroblastotic placenta (Fig. 1).

On March 8, 1945, a test for blocking antibody in the patient's serum was negative. At this time the patient was about five weeks pregnant (her third pregnancy), the last menstrual period being Jan. 28, 1945. On May 23, 1945, the blocking antibody was again found, and this increased in amount until June 1, 1945. On June 6 the patient reported she had not felt life for four days, and on July 5 labor was induced by the use of a Voorhees bag. On July 7, the third pregnancy terminated by spontaneous delivery of a 290-Gm. macerated male fetus. Autopsy was not done. Placental weight, 300 grams. The ratio of placental weight to that of fetus was 1:1. Pathologist's report: abortion.

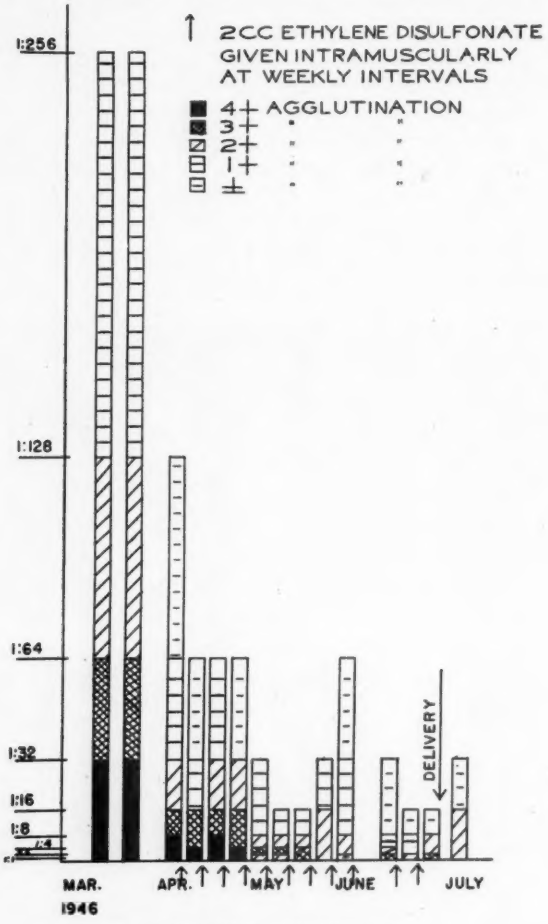


Fig. 2.—Conglutinin titrations, Case 1.

On March 15, 1946, the patient reported to clinic stating that her last menstrual period had been Oct. 7, 1945. The estimated date of confinement was July 14, 1946. The Rh conglutinin titers during the course of this pregnancy are shown in Fig. 2 along with the dosages of ethylene disulfonate administered. Agglutinating antibody was never found in the serum. On June 29, 1946, the fourth pregnancy terminated by spontaneous onset of labor with delivery of a living 3,380 Gm. female after a labor of fifteen hours. Physical examination of the infant was entirely normal. The average daily blood counts are shown in Table I. The infant was group A Rh positive. No Rh antibodies were found in the cord blood. Prothrombin time 25/26 seconds.

The infant was discharged from the hospital on its tenth day of life weighing 150 Gm. above birth weight. The clinical course of the infant during its hospital stay and subsequently was entirely normal. The infant appeared only slightly icteric on its third day of life, but this entirely disappeared within two days. Placenta: weight 680 grams. Ratio of placental weight to that of fetus 1:5. Pathologist's diagnosis: normal cord and placenta (Fig. 3).

CASE 2.—Mrs. M. A., a 30-year-old para iii, gravida iv. Wassermann reaction was negative. The patient's obstetric history is summarized in Fig. 4.

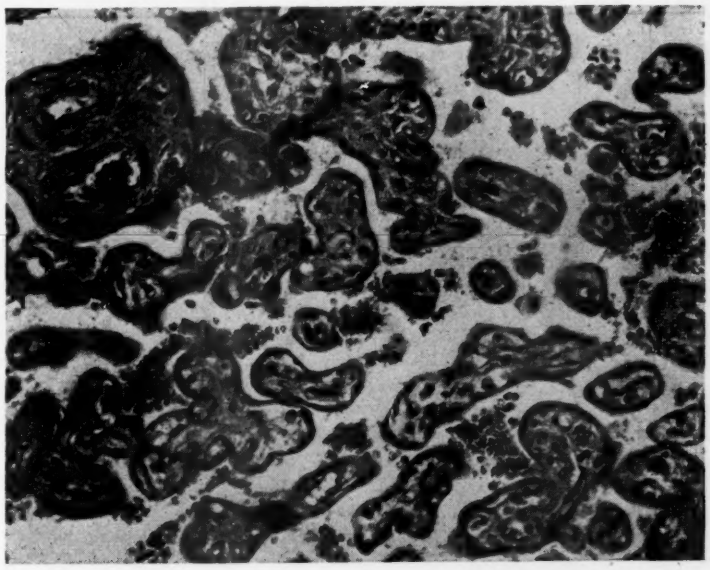


Fig. 3.—Photomicrograph of placenta from Case 1. Infant born in 1946. Normal. Mature red blood cells in small vessel near top. Normal villi. (×210.)

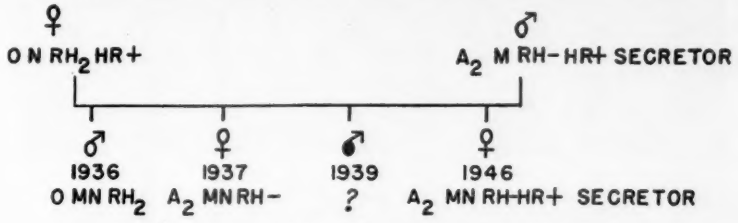


Fig. 4.—Obstetric history Case 2 (Mrs. M. A.)*

*We are indebted to Dr. Alexander S. Wiener for carrying out the Rh typing and Hr tests in this case.

The first two infants were clinically normal. The third pregnancy terminated one week past term with the delivery of a living, 2,730 Gm. male infant. It is of interest that the infant was relatively small in spite of the fact that it was delivered at full term. At the time of delivery the amniotic fluid and vernix caseosa were golden yellow colored, although the sclerae were not icteric. No note was kept concerning the placenta, nor were microscopic sections of the placenta made. When the infant was twelve hours old it was noted to be icteric. The spleen and liver were enlarged. Twenty-four hours later there was no improvement in the infant's condition. The icterus index at this time was 240 units. Red blood cells, 5.90, hemoglobin, 22.0 Gm., white blood cells, 23,000. Smear showed "definite increase in erythroblasts." Infant transfused

with 100 c.c. of mother's blood without reaction. Splenectomy was considered. However, the infant continued to do poorly, and shortly after the transfusion had a convulsive seizure. These seizures became progressively more severe and frequent and the baby died fifty-three hours after birth. Clinical diagnosis: icterus gravis.

The anatomic diagnosis following autopsy included among others, "Question of erythroblastosis fetalis." The pathologist makes a further note: "N. B.

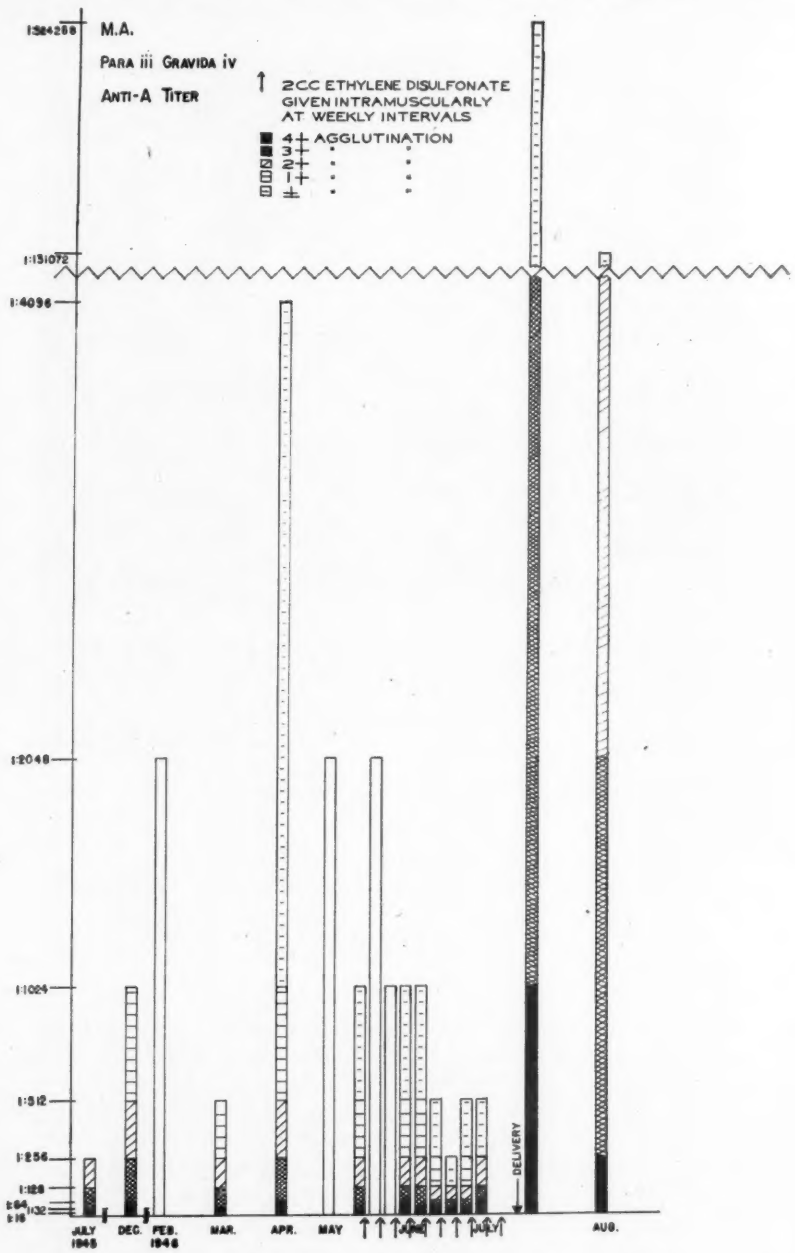


Fig. 5.—Anti-A titrations Case 2.

TABLE I. COMPARISON OF BLOOD STUDIES, OF THE THREE INFANTS DISCUSSED, WITH NORMAL VALUES AS PRESENTED BY CHUINARD, OSGOOD, AND ELLIS[15]

DAYS	AVERAGE RED BLOOD CELLS (GIRLS)				AVERAGE HEMOGLOBIN (GIRLS)			
	NORMAL	CASE 1	CASE 2	CASE 3	NORMAL	CASE 1	CASE 2	CASE 3
1	4.65	5.23	5.59	4.61	17.01	22.00	21.00	16.7
2	4.71	4.53	4.46	4.28	17.58	18.30	18.30	15.9
3	4.95	4.44	5.20	3.74	17.28	16.90	18.35	15.0
4	4.56	4.73	5.38	4.13	17.45	16.90	19.10	15.0
5	4.56	4.87	4.75	3.76	15.39	17.20	18.25	15.0
6	4.53	4.98	5.10	3.50	15.99	17.20	18.00	14.2
7	4.07	4.52	5.10	3.10	14.10	16.70	17.50	12.6
8	4.52	4.22	4.80	3.23	16.02	16.20	18.00	13.1
9	4.58			2.70	15.48			11.3
10	4.28		4.95	3.60*	14.88		17.60	13.8*
11				3.30*				12.3*
12		4.25		2.60*		16.60		11.0*
13				3.30*				13.3*

*Following transfusion.

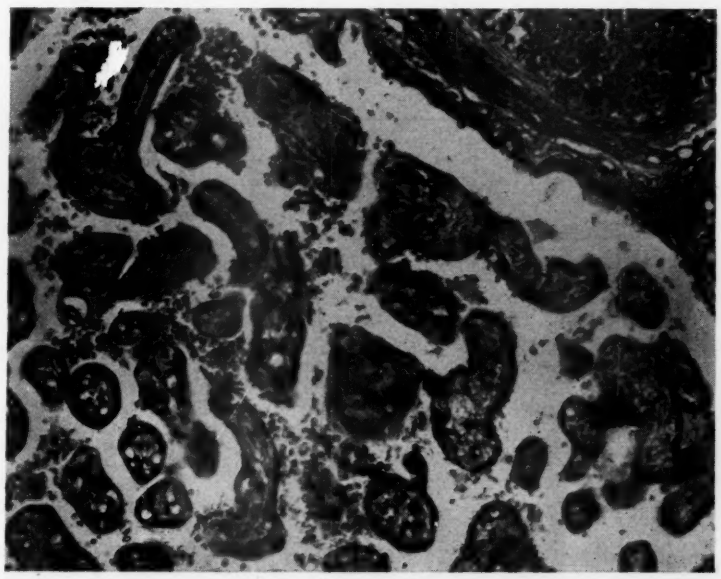


Fig. 6.—Photomicrograph of placenta from Case 2. Infant born 1946. Normal. Normal red blood cells in large vessel. Normal villi. Normal vascularity. (×210.)

The findings here are compatible with erythroblastosis fetalis, but the diagnosis must rest more on the post-mortem peripheral blood morphology."

The obstetrician made a note in the patient's chart as follows: "This patient's baby died of erythroblastosis, confirmed clinically by Dr. S. W. Clausen, professor of pediatrics, and also at autopsy. In view of the likelihood that all subsequent pregnancies may result in the same condition, it seems wise to give contraceptive advice."

In July, 1945, the patient consulted the author regarding future pregnancies. She was found to be group O Rh positive. Anti-A titer 1:256 (Fig. 5). She was seen again in December, 1945, at which time she reported her last menstrual period as Oct. 8, 1945. Her estimated date of confinement was July 15, 1946. Both A and B antibody titrations were carried out during the remainder of this patient's pregnancy. Only the anti-A titers are shown in Fig. 5, since

only they are significant. The dosages of ethylene disulfonate administered are also shown in Fig. 5.

On July 20, 1946, this fourth pregnancy terminated by spontaneous onset of labor with delivery of a living, 3,880 Gm. female infant after a labor of seven hours. Physical examination of the infant was entirely normal. The average daily blood counts are shown in Table I. Blood typing: group A_2 MN Rh negative, Hr positive. Secretor. Anti-A titer on cord blood 1:64. Prothrombin time was not ascertained.

The infant was discharged from the hospital on its tenth day, weighing 160 Gm. above birth weight. The clinical course of the infant during its hospital stay and subsequently was entirely normal. No clinical icterus was noted by the author and several other observers. However, one observer questioned the presence of icterus on the infant's fourth day of life, at which time an icterus index was 60 units per 100 c.c. of blood. Placenta: weight 670 grams. Ratio of placental weight to that of the fetus 1:5.8. Pathologist's diagnosis: normal cord and placenta (Fig. 6).

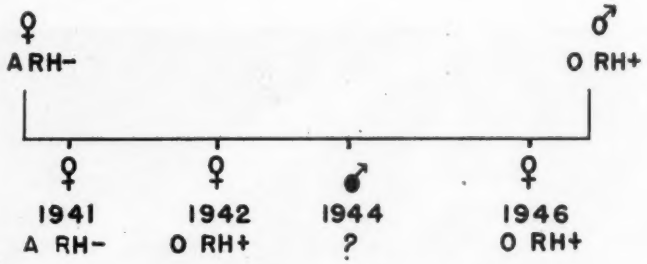


Fig. 7.—Obstetric history Case 3 (Mrs. V. S.)

TABLE II. BLOOD STUDIES ON INFANT, CASE 3

DATE	TIME	RED BLOOD CELLS MILLIONS PER MM.³	HEMOGLOBIN GRAMS PER 100 C.C.	WHITE BLOOD CELLS PER MM.³	I. I. UNITS PER 100 C.C.	REMARKS
9/28/46	11:00 P.M.					Birth
9/29/46	12:30 A.M.	5.01	17.9	19,500	30	Smear—6 normoblasts per 100 white blood cells
9/30/46	10:00 A.M.	4.40	16.0			Prothrombin time 26/18
10/ 1/46		3.74	15.0	11,650		Smear—1 erythroblast
10/ 2/46	11:00 A.M.	4.17	16.5		100	Definite icterus present
10/ 3/46	8:30 A.M.	4.00	15.5		88	
10/ 4/46	8:30 A.M.	3.60	15.0	13,250		
10/ 5/46	9:00 A.M.	3.20	12.7			
10/ 6/46	8:45 A.M.	3.33	13.0			
10/ 7/46	9:00 A.M.	2.70	11.3			Transfusion 70 c.c. group O Rh- blood
10/ 8/46	8:30 A.M.	3.60	13.8			Transfusion 50 c.c. group O Rh- blood
10/ 9/46	9:00 A.M.	3.30	12.3		54	Icterus nearly gone
10/10/46	10:00 A.M.	2.60	11.0			Transfusion 70 c.c. group O Rh- blood
10/11/46	2:00 P.M.	3.30	13.3			
10/12/46	9:00 A.M.	3.00	12.0			
10/13/46	11:30 A.M.	3.30	12.0			
10/14/46	2:00 P.M.	2.70	11.0			
10/15/46	9:00 A.M.	2.60	10.5			Transfusion 70 c.c. group O Rh- blood
10/16/46	2:00 P.M.	3.60	13.5			
10/22/46		3.90	12.0			

CASE 3.—Mrs. V. S.* A 27-year-old para iii, gravida iv. Wassermann reaction negative. The obstetric history is shown in Fig. 7.

The first two pregnancies were entirely normal, as were the infants. The expected date of delivery for the third pregnancy was Nov. 20, 1944. The pregnancy progressed in a normal manner until the patient's visit to her

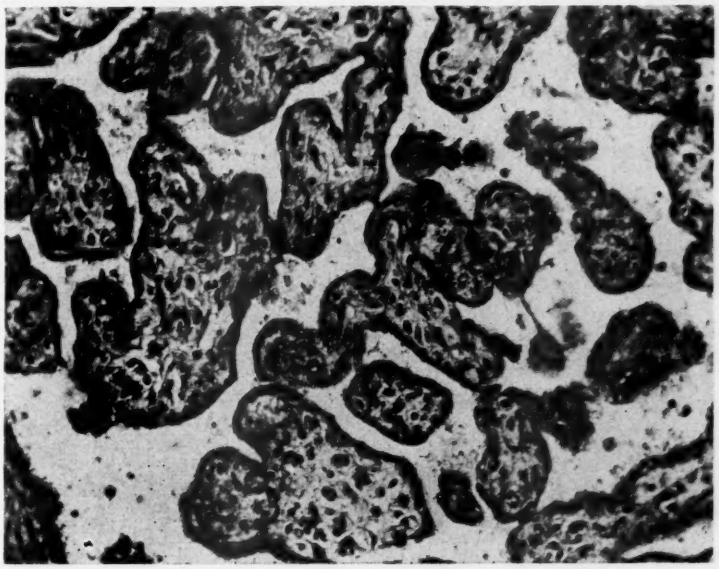


Fig. 8.—Photomicrograph of placenta from Case 3. Infant stillborn 1944. Villi large, thick, blunt. Persistence of double layered trophoblast in areas. Vascularity diminished. (×210.)

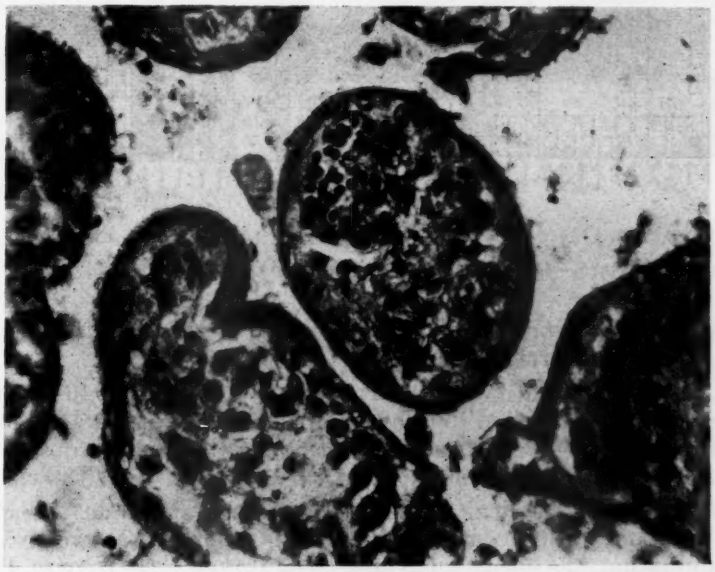


Fig. 9.—Same case as Fig. 8. Villus in center shows vessel full of nucleated red blood cells. It is large. There is persistence of Langhans' layer. Stroma is edematous. (×430.)

*This patient was delivered of her second and third pregnancies at the Genesee Hospital, Rochester, New York. We are indebted to that institution for the information we have concerning the third pregnancy, and to Dr. Jacob Epstein for allowing us to study the patient during her recent pregnancy.

obstetrician nine days before term, at which time he was unable to hear the fetal heart. Three days later the patient went into labor spontaneously and delivered a 3,370 Gm. stillborn male infant. No definite diagnosis could be made by the pathologist following autopsy because of autolysis of the organs. The protocol states, however, that there was among other things "marked edema of the subcutaneous tissues; congestion and intra-alveolar hemorrhages."*

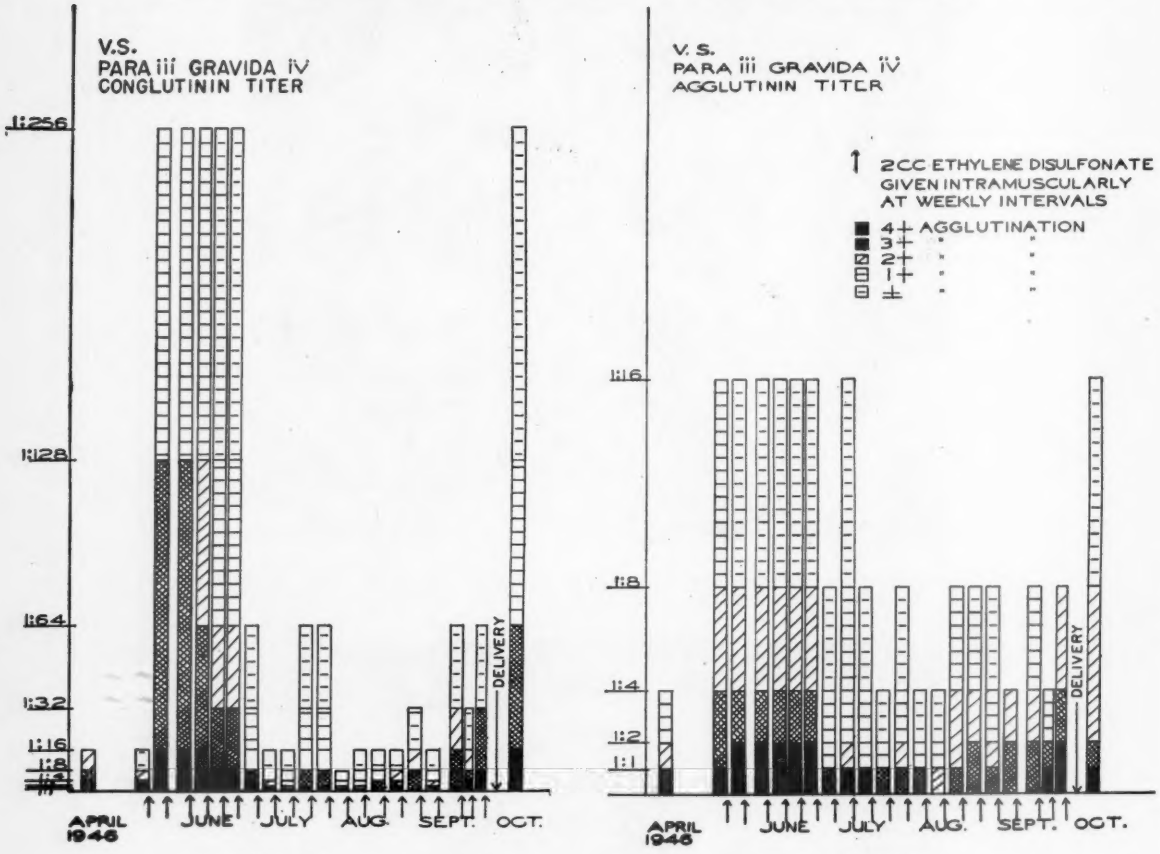


Fig. 10*A*. Fig. 10*B*.

Fig. 10.—Conglutinin and agglutinin titrations Case 3.

The pathologist felt that the microscopic picture of the placenta was "indicative of fetal erythroblastosis" (Figs. 8 and 9).

The patient consulted her obstetrician on Apr. 27, 1946 regarding her fourth pregnancy, the expected date of confinement of which was Sept. 27, 1946. The Rh-antibody titers obtained and the ethylene disulfonate dosages administered this patient during the remainder of this pregnancy are shown in Fig. 10.

On Sept. 28, 1946, medical induction of labor resulted in the spontaneous delivery of a living 3,490 Gm. female infant following a twelve-hour labor. Physical examination was entirely normal. The infant was group O, Rh positive.

*Sections of lung and kidney from this infant were sent to Dr. Edith Potter following her recent publication on the diagnosis of hemolytic disease of the newborn in the macerated fetus,[14] and she reports as follows: "The presence of the large immature red cells in the lung is not as marked as in some cases, but I believe they are found in sufficient numbers to make a presumptive diagnosis of erythroblastosis. The blood within the larger vessels also shows a higher incidence of nucleated cells than is normally found. The vessels in the kidney likewise show nucleated cells in greater numbers than normal."

Cord blood revealed an Rh conglutinating antibody titer of 1:128. This had fallen to 1:64 in venous blood obtained by heel puncture on the infant's ninth day of life. In neither case was agglutinating antibody found. Only the more pertinent blood studies done on this infant are presented in Table II.

On Oct. 17, 1946, the infant's nineteenth day of life, it was discharged from the hospital weighing 520 Gm. above birth weight. The clinical course of the infant during its hospital stay was typically one of hemolytic disease of the newborn. At the time of discharge, the baby appeared to be entirely normal. Its subsequent course has been uneventful.

Placenta: weight 550 Gm. Ratio of placental weight to that of the fetus 1:6.3. Pathologist's diagnosis: Normal cord and placenta (Fig. 11).

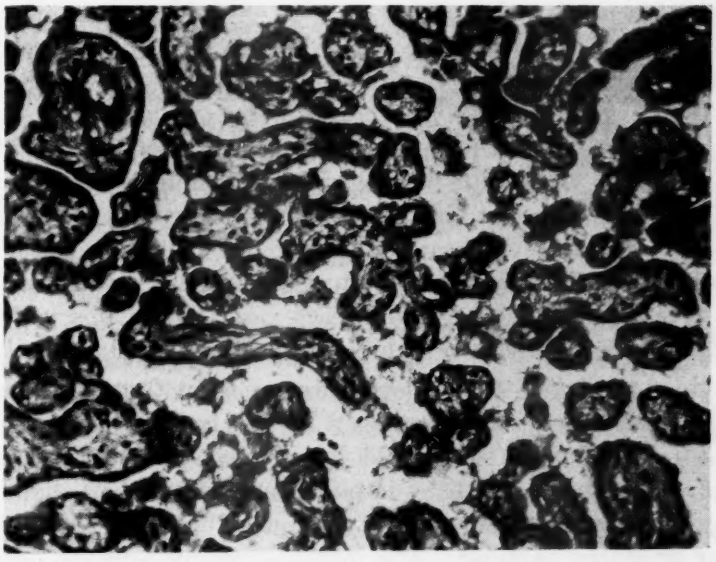


Fig. 11.—Photomicrograph of placenta from Case 3. Infant born 1946. Normal. Placenta normal. (×210.)

Discussion

The author has attempted to prove that in each of the three cases presented the patient had, prior to the present study, given birth to one or more infants suffering from hemolytic disease of the newborn. To this end extensive case histories and photomicrographs of placentas have been presented. If it is conceded by the reader that in each case a history of hemolytic disease of the newborn exists, then he must likewise concede that all subsequent pregnancies should result in the delivery of an infant with hemolytic disease of the newborn, provided certain criteria are fulfilled. If this is not so, then we must abandon our entire concept of the etiology of hemolytic disease of the newborn. In Cases 1 and 3, in order for this to happen, it would be necessary that subsequent infants be Rh positive. In Case 2 it would be necessary that the infant belong to group A and that the mother again be sensitized to the A factor, as she was in her previous pregnancy. In each instance, it has been demonstrated that these criteria have been fulfilled. One can conclude, therefore, that in each case, the most recent pregnancy should have resulted in the birth of a

baby suffering from hemolytic disease of the newborn. That this did not happen is obvious from the results presented. The infants in Cases 1 and 2 were clinically normal. In Case 3, the infant very obviously had hemolytic disease, but in a form amenable to treatment and mild enough that it survived following transfusion. This occurred, in spite of the fact that the previous pregnancy of this patient resulted in the birth of a stillborn, possibly hydropic infant.

In Cases 1 and 2 there was no evidence clinically that the infants were not normal. Physical examination was entirely normal at birth and remained so throughout the period of observation. In both instances there was possibly slight icterus on the third and fourth days of life, respectively, but no more than one sees frequently and interprets as a very mild physiologic jaundice. In each instance this very slight icterus was gone within two days. In both cases the infants took their feedings well, gained satisfactorily, and were discharged from the hospital above birth weight.

Table I lists the daily average red blood cell and hemoglobin values of all infants and compares them with normal values as published by Chuinard, Osgood, and Ellis.[15] In Cases 1 and 2 the initial levels for both red blood cell and hemoglobin were higher than normal, possibly due to the fact that the cords were not clamped until pulsations had stopped, and there was consequently a drop in the levels on the second day in each case. From this point on, however, the values were equally high or higher than the normal values listed.

In case three the findings were not as dramatic, but the results were equally satisfactory, in that this patient now has a normal healthy baby, when it could rightfully be expected that she should have delivered another stillborn and probably hydropic infant. The baby in question began to show slight icterus on its third day of life, and by the fourth day was definitely icteric. At no time was the liver or spleen palpable. The infant appeared well and took its feedings satisfactorily resulting in a good weight gain so that at the time of discharge from the hospital it was far above birth weight. The average daily red blood cell and hemoglobin levels of this infant (Tables I and II) gradually fell until on the ninth day of life, transfusion seemed to be indicated. It was then found necessary to give the infant a total of 260 c.c. of Rh-negative blood before a satisfactory level was maintained.

From the foregoing, one can deduce that the three infants under discussion should have had hemolytic disease of the newborn, but that only one of them did suffer from that disease, and that one only in a form mild enough that it was entirely amenable to transfusion therapy.

It is essential now that we review the antenatal care of the patients in these three cases. This consisted of repeated intramuscular injections of ethylene disulfonate in a dilution of $1:10^{-15}$ in distilled water, along with close observation of the titer of Rh antibody and alpha agglutinin. From Figs. 2, 5, and 10, one can see that in each instance the offending antibody titer fell from relatively high levels to relatively low ones. Case 3 differs from the first two in this regard in that the level did not remain low, but tended to rise, not only in the total number of test tubes in which agglutination was detectable, but in the degree of

agglutination present in each tube. This would seem to be significant, since the patient in this case delivered an infant with hemolytic disease of the newborn, whereas the patients in the first two cases delivered normal infants.

In a large series of cases in which we have had the opportunity to follow antibody titers during pregnancy, we have never observed a fall in titer, as was noted in these cases, except when the infant dies in utero. Our experience has been that the level either remains static or rises gradually. This has been the experience of others.[16]

What, then, brought about this fall? It must be one of two things; either ethylene disulfonate or distilled water. It does not seem possible that the minute quantities of ethylene disulfonate given could have any effect upon the antibody producing mechanism of the body. How could the distilled water do this? One possible answer is that as the result of the injection of such an unphysiologic solution into muscle tissue, there is a certain amount of tissue damage. This in turn could cause the liberation of an "*x*" substance which when picked up by the blood stream would neutralize all the circulating antibody, and thus bring about a fall in antibody level. Another possibility would be that this "*x*" substance would attract all antibodies to the site of injury, and likewise deplete the serum titers. Repeated injections of the offending agent would tend to make the process continuous.

We have observed as have others that the absolute level of titration of the Rh antibody bears little or no relationship to the severity of the disease in the newborn. In view of the present observations, it is felt now that that statement is only a partial truth. We believe now that the total antibody level when it is coupled with the amount of agglutination per test tube may be of definite help in prognosticating the seriousness of the disease in the newborn. For example, a serum carrying a titer of 1:64 in which only the first tube shows 4+ agglutination is not as potent a serum as one carrying a titer of 1:64 in which five of the tubes show 4+ agglutination. Figs. 1 and 10 illustrate this point. The technique of performing the titration tests must, of course, be kept uniform in all respects. In addition, it would seem that the length of time the patient carries a high titer of antibody is more important than the height of the titer of the antibody. So that when one attempts to prognosticate the severity of hemolytic disease of the newborn, he should consider three factors; (1) the length of time before term that antibody appears in the maternal serum, (2) absolute height of antibody, and (3) degree of agglutination per test tube noted when titration is being carried out. This proposition is based on the fact that in Cases 1 and 2 the high titer and high degree of agglutination (4+ and 3+), were carried for only a relatively short time, while in Case 3, although the high titers were present only a relatively short time, still the degree of agglutination per tube (4+ and 3+) remained elevated for a considerably longer period. When reviewing the individual tube agglutination for Case 2 (Fig. 5), it must be kept in mind that the alpha agglutinin is a natural one for this patient and that its usual titer of 1:256 is illustrated in the first column to the left of the figure. Apparently it is not possible to reduce the total titer or degree of agglutination per tube below those values observed in the pre-pregnant state.

The conclusion, then, seems justified that as a result of the intramuscular injection, as given, two infants were spared from hemolytic disease of the newborn, while the third had the disease in a milder form than would normally have been expected.

No other patients have been handled in the manner described. However, further studies are being made on the use of distilled water in this connection.

It is of interest to note that no marked change in antibody level was apparent until four to six injections had been given. The significance of this is not clear. It is also of interest that in each case there was a rise in antibody level on the eighth to tenth postpartum day. This reaction has been described by others. It is especially marked in Case 2 (Fig. 5).

In Case 3 when it was definitely established that the antibody was rising again as the patient approached term an attempt was made to arrest this by increasing the frequency of injections, but to no avail. It is entirely possible that had labor been induced four to six weeks before term, an entirely healthy, though premature infant would have resulted. Instead, the patient was allowed to go to full term at which time induction of labor was carried out.

It is interesting to note that in Case 2, although the infant belonged to group A, the cord blood carried an anti-A titer of 1:64. In Case 3 the Rh conglutinating antibody in cord blood was 1:128, and still remained high in venous blood drawn from the infant nine days later.

Case 2 is one more to add to the list of hemolytic disease of the newborn due to A-O or B-O incompatibility. Boorman, Dodd, and Mollison,[17] La Vake,[18] Polayes,[19] and Wiener[20] have reported other cases. This is similar to some reported by Wiener in that the infant was a secretor, as they were in some of his cases.

It should be stated that very rarely will one find Rh antibodies in the maternal serum in goodly amounts only to have that patient later deliver a healthy Rh-positive infant. In fact the author has reported two such cases.[6] In neither case, however, had the patient previously delivered an infant suffering from hemolytic disease nor had this been so in the other similar cases reported.[21, 22] It is on this fundamental point that these cases differ from those described in this presentation.

Summary

Three cases are presented in which an attempt was made to prevent hemolytic disease of the newborn by means of intramuscular injections of ethylene disulfonate in distilled water into the mother ante partum.

In two of the cases normal infants were born while in the third case the infant suffered from hemolytic disease.

It is suggested that some nonspecific tissue reaction may bring about a lowering of the serum antibody level, and thus prevent or modify the disease in the newborn.

A more suitable plan for aiding in the prognostication of hemolytic disease of the newborn is outlined.

References

1. Kariher, D. H.: Discussion, Philpott et al.: Am. J. Obst. & Gynec. **52**: 926, 1946.
2. Kariher, D. H.: Virginia M. Monthly **73**: 347, 1946.
3. Levine, P.: New York State J. Med. **45**: 296, 1945.
4. Kariher, D. H.: Unpublished data.
5. Wiener, A. S., and Sonn, E. B.: Am. J. Dis. Child. **71**: 25, 1946.
6. Kariher, D. H., and Miller, D. I.: Am. J. Med. Sc. **212**: 327, 1946.
7. Evans, G., Bodman, J., and Maisin, J. H.: Med. Press. & Circ. **203**: 457, and 476, 1940.
8. Fisk, R. T., Small, W. S., and Foord, A. G.: J. Allergy **15**: 14, 1944.
9. Council on Pharmacy and Chemistry, A. M. A.: J. A. M. A. **131**: 1495, 1946.
10. Wiener, A. S.: Blood Groups and Transfusions, ed. 3, Springfield, Ill., 1944, Charles C Thomas, p. 17.
11. Wiener, A. S.: J. Lab. & Clin. Med. **30**: 662, 1945.
12. Carter, B. B., and Loughrey, I.: Am. J. Clin. Path. **15**: 575, 1945.
13. Wiener, A. S.: Proc. Soc. Exper. Biol. & Med. **56**: 173, 1944.
14. Potter, E. L.: Arch. Path. **41**: 223, 1946.
15. Chuinard, E. G., Osgood, E. E., and Ellis, D. M.: Am. J. Dis. Child. **62**: 1188, 1941.
16. Philpott, N. W.: Personal communication.
17. Boorman, K. E., Dodd, B. E., and Mollison, P. L.: J. Obst. & Gynaec. Brit. Emp. **51**: 1, 1944.
18. La Vake, R. T.: Journal-Lancet **63**: 51, 1943.
19. Polayes, S. H.: Am. J. Dis. Child. **69**: 99, 1945.
20. Wiener, A. S.: Personal publication, 1946.
21. Dockeray, G. C., and Sachs, H.: J. Immunol. **48**: 241, 1944.
22. Goldbloom, A., and Lubinski, H.: J. Pediat. **28**: 83, 1946.

A STUDY OF TWO TRANSFUSION DEATHS DUE TO Rh INCOMPATIBILITY

BRUCE F. P. WILLIAMS, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, Cornell University Medical College and The New York Hospital)

SINCE the discovery of the Rh antigen in 1940 by Landsteiner and Wiener, the medical profession has become acutely aware of the importance of this factor in hemolytic disease of the newborn. Only in recent years, however, has the significance of the Rh antigen in transfusion reactions been appreciated. Much has been written concerning the need of Rh compatibility tests prior to transfusion with whole blood, and the necessity for employing Rh-negative blood in transfusing Rh-negative individuals. Yet, little information is available as to methods of therapy once a transfusion has been given with incompatible blood and a reaction occurs.

It is the purpose of this paper to report two deaths attributed to transfusion with incompatible Rh blood. The first death occurred in June, 1944, prior to the development of a definite clinic policy concerning the Rh antigen at the New York Lying-In Hospital, and was the stimulus for its inauguration in August of the same year. Cole has reported in detail the development of this policy with respect to the precautionary and investigatory procedures now employed. The second death occurred in 1945, attributed to an error in the Rh typing.

Transfusion Deaths Due to Incompatible Rh Blood

CASE 1.—The patient was a 32-year-old para iii, gravida vi, who was admitted to the obstetric service in 1944 at seven months gestation with a history of antepartum bleeding. Her obstetric history revealed one spontaneous abortion and three normal deliveries prior to the delivery of a deadborn, macerated, erythroblastotic (?) fetus at six months in 1940. When first examined in the hospital, the fetal heart could not be heard, and a sterile vaginal examination four days later showed the cervix to be three centimeters dilated with bulging membranes. The membranes were ruptured, no placenta was identified, but labor did not ensue. Because of continued bleeding, operative intervention was decided upon. Re-examination revealed the presence of a marginal placenta previa with the cervix five centimeters dilated. An internal podalic version, breech extraction, and manual removal of the placenta were performed. The infant was a 750 Gm. macerated male. During the operation the patient suffered a blood loss of 800 c.c., and a transfusion of supposedly compatible blood was given. Shortly after the transfusion was completed a reaction occurred which was characterized by chills, fever to 39.2° C., and shock. On the day following the transfusion there was an icteric tint to the sclera and skin, and it was noted that the patient had not voided since delivery. Catheterization yielded but 10 c.c. of urine. Determination of the patient's Rh type showed her to be Rh negative, while the donor was Rh positive.

The decision was made to alkalinize the patient and force fluids in the form of hypertonic glucose by mouth and by vein in an attempt to stimulate the kidneys both by massive hydration and hyperglycemia. Accordingly, the intravenous intake included 3,050 c.c. of 20 per cent glucose supplemented with 50 per cent glucose and M/6 lactate to maintain urine alkalinity. The blood nonprotein nitrogen was recorded as 78.4 mg. per cent. Examination of the urine failed to demonstrate hemoglobin or red cells. On the third post-transfusion day (hereafter to be referred to as PT day) the output was only 77 c.c. despite an intravenous intake of 3,500 cubic centimeters. Vasodilators in the form of aminophylline and caffeine were administered with no demonstrable effect. As a result of the daily use of M/6 lactate the carbon dioxide combining power of the blood rose to 90+ volumes per cent and it was discontinued. By now the patient was clinically worse. She was restless, nauseated, and drowsy. All oral feedings and fluids were promptly expelled, so that nutrition had to be maintained by parenteral feedings. An oxygen tent relieved the patient greatly.

On the fifth PT day the output had risen to 120 c.c., with an intake of 2,000 c.c. Edema of the face and extremities was marked, although the lungs were clear. Intravenous calcium chloride was administered to combat the alkalosis. By the eighth PT day the output had risen to 445 c.c., although the nonprotein nitrogen was now 114 mg. per cent. Clinically, the patient was critically ill. Generalized edema was marked; fine moist râles were heard at the bases, as well as coarse rhonchi through the lung fields; the breath was typical of nitrogen retention; and the patient was semicomatose but afebrile. As a final resort, intravenous sucrose was employed to stimulate the kidneys, without beneficial results being observed.

The next day (PT nine) the temperature rose to 38.4° C. and penicillin was started. It was the impression that the patient had a terminal pneumonia with respirations labored and shallow. The urinary output had increased to 620 c.c. In the early morning of the tenth PT day the patient went into extremis and expired. Blood chemistries drawn immediately prior to death revealed a nonprotein nitrogen of 159 mg. per cent, in spite of the steadily increasing output.

Autopsy showed that all the body cavities were partially filled with fluid. The right pleural cavity contained 500 c.c. of straw-colored fluid and the left, 250 c.c. The tissues were markedly edematous. Grossly, the lungs showed the presence of multiple areas of consolidation with large amounts of expressible fluid in the alveoli and bronchioles. The right and left kidneys weighed 300 and 325 Gm., respectively, and were larger than normal. The capsules stripped easily, exposing a pale gray, smooth cortical surface with scattered punctate areas of hemorrhage. The cut surfaces revealed a well-differentiated medullary area with scattered hemorrhages present throughout the cortices. Microscopically, the tubules in the upper medullary region were found to contain some blood cells and hemoglobin casts. Throughout the stroma of the kidney numerous lymphocytes and scattered neutrophils were present. Bowman's capsule surrounding many of the glomeruli was distended and filled with some pink precipitate.

The intake, output, and changes in the blood chemistry are tabulated in Table I.

Nonprotein Nitrogen: Two days following the transfusion the nonprotein nitrogen was elevated to 78 mg. per cent. Despite fluid therapy and an increasing urinary output, the nonprotein nitrogen slowly rose to 160 mg. per cent by the day of death. Similarly, the blood urea nitrogen showed a like pattern, rising from 63 mg. per cent to 87 mg. per cent.

TABLE I. LABORATORY STUDIES OF FIRST PATIENT DYING FROM A TRANSFUSION OF INCOMPATIBLE RH BLOOD

PT DAY	B.U.N.	SUGAR	CO_2	PROTEIN	N.P.N.	URIC ACID	HEMOGLOBIN	OUTPUT	INTAKE
1	--	---	--	--	--	---	8.5	0	3,400
2	--	450	52	--	78	6.0	6.0	50	3,050
3	63	---	90+	--	77	9.1	--	77	3,500
4	68	---	90+	--	79	9.2	--	100	2,000
5	--	---	--	--	--	--	6.0	120	1,900
6	73	---	84	--	100	16.4	--	125	3,000
7	77	---	80	--	94	14.3	--	170	2,000
8	--	---	60	--	103	14.6	--	445	3,050
9	87	140	66	4.8	115	15.8	--	620	60
10	--	---	--	--	160	17.7	--	---	----

Carbon Dioxide Combining Power: Three hours prior to transfusion the patient received 3 Gm. of sodium bicarbonate by mouth. On the first PT day she received a total of 8 Gm. of oral sodium bicarbonate and 1,000 c.c. of intravenous M/6 lactate; and on PT day two 12 Gm. of oral bicarbonate of soda, and 2,000 c.c. of intravenous M/6 lactate were given. At that point the CO_2 combining power was found to be 90+ volumes per cent. Alkalinization was then abandoned, and all fluids thereafter were either 20 per cent or 50 per cent glucose. By PT day seven the CO_2 combining power was still 80 volumes per cent, so calcium chloride (10 c.c. of a 5 per cent solution) was administered twice that day. Subsequent readings were within normal range. Clinically, there were no signs of the marked alkalosis.

Uric Acid: A rise in the uric acid value occurred which more or less paralleled the rise in nonprotein nitrogen.

Water Balance: On admission to the hospital the patient weighed 58.8 kilograms. Delivery resulted in the loss of approximately 3.0 kilograms of weight,* yet at autopsy the patient weighed 60.0 kilograms. Thus, the patient gained approximately 4.2 kilograms while she was in the hospital, the majority of which was presumably represented by retained fluid.

Urine: Despite the marked alkalosis as exhibited by blood studies, the urine pH never exceeded 7.75, the usual pH being in the vicinity of 7.5. Repeated microscopic examinations failed to show the presence of red cells or cellular debris. The output steadily increased from 0.0 on PT one to 620 c.c. the day before death. The urine was consistently amber in color and usually clear, although on several occasions slight turbidity was noted.

Comment.—It is apparent in this case that the renal shutdown occurred as the result of an Rh-negative individual being transfused with Rh-positive blood, and that the accident would have been avoided had the patient been Rh typed prior to transfusion. The patient had been sensitized by previous pregnancies, for she had no history of previous transfusion therapy. The oliguria appeared immediately. The treatment consisted of hydration and alkalization. Despite a CO_2 combining power of 90+ volumes per cent, there was no diuresis, nor did the urine become markedly alkaline. The cause of death was probably the massive terminal pulmonary infection. Pulmonary edema was probably no more than a secondary cause, for the greatest amount of retained fluid at death could not have been more than 4.2 kilograms. It is unlikely that this small volume could produce primary pulmonary edema. The kidney lesions were typical of transfusion reaction kidneys wherein considerable difficulty is experienced in locating lesions or casts. The greater part of the kidney parenchyma appeared normal.

CASE 2.—The patient was a 33-year-old, para iii, gravida iv, who was admitted to the obstetric service prior to the onset of labor. The past obstetric

*Fetus, 760 Gm.; blood, 800 c.c.; amniotic fluid, 1,000 c.c.; and placenta, 410 Gm.

history revealed that she had had three normal full-term deliveries. There was no positive history of hemolytic disease, although the last infant, born in 1944, became slightly jaundiced twenty-four hours after birth.

In the present pregnancy the patient was registered late in the thirty-fifth week of gestation in December, 1945. The initial examination was unremarkable; her blood was typed as group A and Rh positive. An anemia was present which did not respond to the usual therapy, so that admission to the hospital in the thirty-ninth week of pregnancy was advised. On admission to the hospital she was found to have a hemoglobin of 8.0 Gm. and a volume of 30 mm. Thus, on the following day a transfusion of 500 c.c. of group A, Rh positive, supposedly compatible blood was administered. There was no reaction until approximately two hours after the discontinuance of the transfusion, at which time the patient complained of chilly sensation, became nauseated, and vomited. Soon after this she began to talk incoherently and her face became markedly flushed. No icterus was demonstrable. Morphine and atropine were given, and shortly afterwards an infusion of M/6 lactate was started as well as oral bicarbonate of soda.

On the evening of the first PT day 20 c.c. of dark brown urine was passed which was guaiac positive for blood. By the second PT day the patient had passed a total of 70 c.c. of urine. The blood bank then rechecked the Rh of the patient and found her, contrary to their initial report, to be Rh negative. The patient was placed in an oxygen tent and local heat was applied externally to the kidney areas. Intravenous fluids in the form of 10 per cent and 50 per cent glucose were started. Aminophylline (0.5 Gm.) was given at three-hour intervals. It was felt that on this regimen diuresis might be facilitated if the blood sugar could be elevated to such a point as to cause spillage of sugar, carrying a corresponding amount of water with it through the kidney tubules, thus washing the tubules free of any possible obstructing casts or cellular debris. In view of the pronounced alkalosis exhibited in Case 1, as well as the marked edema, the sodium ion was restricted so as to minimize the storage of fluid in the extracellular compartment. Hypertonic glucose in distilled water, 6,350 c.c., was administered intravenously over a twenty-four period, and only 170 c.c. of urine was obtained. The blood sugar rose to 223 mg., far below a good renal spillage threshold. On PT day four the urine obtained was four-plus for sugar, so that maximum diuresis from glucose therapy was being achieved, yet the output was only 73 cubic centimeters.

A celiac ganglion block was performed in an attempt to eliminate any possible spasm of the renal vessels, if spasm be present, and possibly increase the blood flow through the kidneys. This procedure failed to produce any increased urinary function. On the fifth PT day it was decided to attempt induction of labor so as to utilize the diuretic phenomenon seen in the early postpartum period. The patient delivered precipitately after two and one-half hours of labor. The infant was a living, normal, 3,580 Gm. female with no signs of hemolytic disease. The infant was found to be Rh positive. The output on that day, despite delivery, was only 21 c.c., the intake 2,500 c.c. By now clinical edema was demonstrable in the extremities, face, and over the sacrum.

By the seventh PT day mercurial diuretics were employed in view of the alarmingly low output, 20 to 30 c.c. per day, as well as a steadily rising nonprotein nitrogen, now elevated to 101. Mercupurin was given in two repeated doses of 1 c.c. each. Catheterization following each injection yielded 12 c.c. and 2 c.c. of urine, respectively. The edema was marked, although, except for an inconstant rhonchus, the lungs were quite clear. There was obvious clouding of the sensorium, and a rather marked diarrhea was present. Despite the employment of mercupurin, the total output for the twenty-four hour period

was only 47 c.c. Mercuhydrin was given in two doses with no demonstrable effect. The blood chlorides had dropped to 391 mg. per cent, so on PT day eleven, 4.5 to 13.0 grams of salt a day were given with the parenteral glucose of 2,500 to 3,000 c.c. a day. Peculiarly enough, the day the salt was added the output increased from 108 c.c. to 908 c.c. Penicillin was started prophylactically in an attempt to prevent the pneumonia previously observed in Case 1.

Clinically, the patient showed marked improvement now. By the thirteenth PT day the urinary output was 3,150 c.c., excelling her intake. The urine had a specific gravity of 1.009 and contained 156 mg. per cent of urea. It was evident that the kidneys were recovering, for their ability to excrete urea had returned, and the nonprotein nitrogen fell from 130 to 111 mg. per cent. The patient could take feedings by mouth and could tolerate being out of the oxygen tent for several hours at a time. The stupor and semicoma had disappeared. Edema was difficult to demonstrate, and examination of the lungs showed them to be clear.

On the fifteenth PT day the clinical picture suddenly and dramatically changed. The pulse became rapid and irregular. Respirations were shallow and rapid. The patient became apprehensive, restless, and finally irrational. Examination of the chest revealed the presence of numerous adventitious sounds, râles and rhonchi throughout. Cyanosis appeared despite the oxygen tent. Pulmonary edema and congestion were obvious and her condition became rapidly grave. Therapy consisted of oxygen by face mask, aminophylline, papaverine, and an attempted but unsuccessful phlebotomy. The patient's course was rapidly downhill and she expired in a few hours.

At autopsy there was a bilateral pleural effusion, 300 c.c. on the right, and 150 c.c. on the left. The lungs were edematous and contained massive areas of consolidation typical of terminal pneumonia. The kidneys were larger than normal, weighing 250 Gm. each. The capsules stripped with ease. Numerous minute, pinpoint spots were seen on the surface, the general appearance being pale and somewhat amber. Microscopically, the kidneys showed a few areas with hemoglobin casts, cellular debris, and unrecognizable coagulum, primarily in the convoluted and collecting tubules. The majority of the kidney parenchyma showed little if any pathologic changes.

Table II shows the blood changes and a record of the patient's intake and output.

TABLE II. LABORATORY STUDIES OF A SECOND PATIENT DYING FROM A TRANSFUSION OF INCOMPATIBLE RH BLOOD

PT. DAY	B.U.N.	SUGAR	CO_2	PROTEIN	N.P.N.	URIC ACID	BLOOD CL.	HEMOGLOBIN	CELL VOLUME	I.V. INTAKE	TOTAL INTAKE	URINE OUTPUT
1	--	---	--	--	--	---	--	--	--	----	----	20
2	84	---	59	--	--	---	--	10.0	--	2,160	5,210	40
3	66	223	62	4.4	82	7.4	479	--	40	6,350	6,450	170
4	65	133	60	5.3	84	8.9	469	--	--	2,450	2,685	73
5	69	190	49	5.5	81	10.6	446	6.5	21	2,335	3,135	21
6	69	190	57	5.3	88	11.1	--	--	31	1,500	2,360	31
7	86	89	51	5.1	101	10.9	423	6.2	--	3,500	3,640	47
8	89	---	45	--	102	13.1	399	--	19	3,500	3,980	38
9	--	---	--	--	---	---	--	--	--	2,300	2,640	105
10	101	77	33	4.8	130	13.1	391	--	21	3,000	4,970	108
11	100	79	41	--	126	12.0	376	--	--	2,500	3,705	908
12	104	75	40	5.0	120	11.6	385	5.7	--	2,500	3,885	1,930
13	107	---	45	5.1	111	13.6	396	--	--	3,150	4,330	3,150
14	102	85	45	--	137	12.3	421	--	21	2,500	4,000	3,850
15	97	---	37	--	---	---	424	8.0	21	2,500	4,150	4,200

Blood Urea Nitrogen and Nonprotein Nitrogen: On the second PT day the blood urea nitrogen was 84 mg. per cent. Slowly, throughout the next thirteen days, it steadily increased, plateauing around 100 mg. per cent during the last five days. The various procedures performer had little effect on this rise. The nonprotein nitrogen similarly rose, although the drop after diuresis had started was noticeable. Although the excretion of urea was observed from PT day eleven and on, there was no marked alteration in the nonprotein nitrogen.

Blood Sugar: It is interesting to note that, although massive glucose therapy was employed, the blood sugar was always below 100 mg. per cent but for the first five days of therapy. After 6,350 c.c. of glucose solutions, containing 1,245 Gm. of glucose, had been given, the blood sugar on PT day three was only 223 mg. per cent and the urine only two-plus for sugar. This utilization on a metabolic basis is unexplainable.

Chlorides: In order to prevent edema and storage of fluid in the extracellular compartment, salt was withheld. However, on PT day eleven, due to the drop in blood chloride level, salt was administered in doses of 4.5 to 13 Gm. a day.

Plasma Proteins: Each time a drop in the plasma proteins was observed 500 c.c. of pooled plasma was given. A total volume of 1,750 c.c. was necessary.

Carbon Dioxide Combining Power: On PT day two the CO_2 was 59 volumes per cent. No alkali was given until the tenth PT day in view of our experience in Case 1. On PT day ten the CO_2 fell to 33 volumes per cent, and a good response was obtained when M/6 lactate was given.

Water Balance: The admission weight was 74.1 kilograms. At delivery the patient lost about 6.0 kilograms.* At autopsy the patient weighed 85.0 kilograms. This represented a weight gain of 16.9 kilograms, all of which probably was retained fluid.

Urine: Table III shows the urine findings during the oliguria and the apparent recovery phase.

From Table III it can be seen that the large volumes of urine passed did contain the usual amounts of urea, even though the specific gravity was low. Yet with this amount of nitrogenous material being passed, the blood levels of nitrogen products still remained elevated. Also, the negative microscopic exam-

TABLE III. URINE EXAMINATIONS OF SECOND PATIENT DYING FOLLOWING TRANSFUSION OF INCOMPATIBLE Rh BLOOD

PT DAY	COLOR	SPECIFIC GRAVITY	REACTION	ALBUMIN	SUGAR	ACET.	URINE U.N.	MICROSCOPIC
0	amber	QNS	acid	0	++	0	--	negative
1	brown	QNS	acid	+++	0	0	--	RBC, casts
2	amber	QNS	7.0	--	+	--	--	--------
3	------	QNS	--	--	++++	--	--	--------
4	amber	QNS	5.5	--	++	--	--	--------
5	amber	QNS	5.5	--	+	--	--	--------
6	straw	QNS	6.9	++	+	--	--	--------
7	yellow	QNS	7.2	+	+	--	--	--------
8	yellow	1.006	--	--	--	--	--	--------
9	------	1.005	--	--	--	--	--	--------
10	cloudy	--	7.6	++	0	0	--	debris
11	cloudy	1.002	alk.	+	0	0	--	--------
12	cloudy	1.002	7.0	tr.	0	0	--	negative
13	cloudy	1.002	6.0	0	0	0	156	negative
14	cloudy	1.009	--	0	0	0	157	negative
15	cloudy	1.009	--	0	0	0	156	negative

*Fetus, 3580 grams; placenta, 640 grams; amniotic fluid, 1,000 grams; blood and lochia, 800 grams.

inations on these same days showed that little if any debris or casts were being removed from the kidney in the diuresis phase.

Comment.—This patient was sensitized by pregnancy, and the reaction was due to Rh incompatibility. Blood drawn on the third PT day for antititer determination showed that the "serum did not contain any blocking antibodies, and the test with serum-suspended cells was negative. Presumably this was due to the so-called negative phase of iso-immunization, and it could be expected that in a week or ten days antibodies would be demonstrable." A blood specimen drawn on PT day ten showed that the "serum was weakly positive for blocking antibodies with a questionable reaction to serum suspended cells." Another qualified examiner reported this same specimen to contain "anti-rh agglutinins of the hyperimmune type or blocking variety which is consistent with a transfusion of incompatible blood." The error in typing was due to testing serum of poor specificity employed at that time. A recheck of other patients whose Rh type had been determined with this same serum showed six additional incorrect reports.

The treatment in this case consisted chiefly of hydration with hypertonic glucose supported with mercurial diuretics, xanthine derivatives, celiac ganglion block, and evacuation of the uterus. The effect of the mercurials as a diuretic agent was unremarkable. The xanthines were ineffectual. It is apparent that the diuresis so commonly seen following delivery cannot and does not occur when urinary suppression is present. Celiac ganglion block likewise failed to alter the picture. Sodium chloride, lactate solution, and plasma were all given as supportive measures to restore and maintain the blood chemical picture as near to normal as possible. The hemoglobin was consistently low. Possible immediate and repeated transfusions of Rh-negative blood might have altered the outcome.

The cause of death was again primarily related to an overwhelming pneumonia, in spite of adequate penicillin therapy for the five days preceding death. Except for one isolated elevation to 38° C. on PT day twelve, the patient's temperature remained normal or subnormal. Pulmonary edema was present terminally and no doubt contributed greatly to the final episode, for at this time the patient was in positive water balance of 17 liters. The renal pathology cannot completely explain the sudden exodus of the patient during the apparent recovery phase of diuresis.

Reports of Similar Cases

Fifteen cases have been selected from the literature for comparison and contrast with the two transfusion reactions presented in this paper. These 17 cases may be briefly summarized in Table IV. All cases selected show proved Rh-negative recipients, and all donors except two were proved to be Rh positive. As to the two exceptions, one donor was represented by pooled red cells; the other by four transfusions of untyped Rh Blood. There was a history suggesting hemolytic disease in 12 cases, and five of the seven deaths occurred in this group. All patients belonged to either group A or group O. In only four cases was toxemia manifested. Chills and fever were the commonest symptoms oliguria the commonest sign. Hemoglobinuria occurred in eight cases, and lumbar pain in five. Vomiting was observed in four cases. In two of the cases shock and air hunger were noted. Clinical jaundice appeared in about one-half of the cases, as did also edema.

The amount of blood given was usually 500 c.c., although several cases received more. In general, those patients sensitized by previous pregnancies ap-

TABLE IV. A SUMMARY OF SEVENTEEN CASES OF BLOOD TRANSFUSION REACTIONS RESULTING FROM RH INCOMPATIBILITY

CASES	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Reference	7	17	2	5	4	4	4	4	1	1	24	24	24	6	6	--	--
Age	35	48	38	36	32	30	32	38	26	29	40	43	34	38	31	32	33
Parity	3	4	6	5	2	2	3	2	3	1	3	4	5	4	6	6	4
Toxemia	0	0	0	+	0	+	0	+	+	0	0	0	0	0	0	0	0
Hemolytic disease			+	?+	?+	+	+	+	+		+	+			+	+	?+
Volume of transfusion	1,000	900	500	100	1,750	1,075	1,250	500	500	500	500	500	1,500	200	250	500	500
X match	+	+	+	+	+	+			+					+	+	+	+
Receiving group	A	A	A	O	A	O	?	?	O	A	A	A	A	O	A	O	A
Donor group	O	A	A	O	A	O	?	?	O	A	A	O	O	?	A	O	A
Receiving Rh	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Donor Rh	+	?+	+	+	+	+	+	+	+	+	+	+	+	?+	+	+	+
Reaction in hours	?	6	1	2/3	?	1/2	1	?	?	Im.	1/4	12	?	Im.	Im.	Im.	2
Lumbar pain	+		+	+												+	+
Chill or fever	+	+		+	+	+	+			+	+	+	+	+	+	+	+
Vomiting		+	+	+													+
Shock														+		+	
Oliguria	+	+	+	+	+	+	+	+	+	?+	+	+			+	+	+
Hemoglobinuria	+		+	+		+			+	+						+	+
Alkalinization		+	+	+			+							+	+	+	+
Day of diuresis		10	8	9			11	7							2	10	11
B. U. N.		135						82								87	107
N. P. N.	161			130			350				160	92			50	160	137
On day		8		11			16	7			9	3			4	10	14
Edema	+	+	+	+			+									+	+
Jaundice		+	+	+	+	+						+	+			+	
On day	?	12	6	10	?	?	?					?	?			1	6
Treatment	Pl.	Cit.		Gl.			Pl.							Gl.	Gl.	Gl.	Pl.
	Bl.	Sul.	?	Pl.	?	?	Bl.	?	S.B.	?	?	?	Bl.	Sa.	Sa.	Sa.	Gl.
	Gl.	Gl.		Bl.			Gl.							ML	ML	ML	Sa.
	Sa.	Sa.		Sa.			ML									Suc.	ML
Recovery				+			+	+	+	+	+	+	+	+	+		
Day of Death	17	12	14		9	10										10	15
Autopsy	+	+	+													+	+

Key: Bl. = Rh negative blood; Cit. = sodium citrate; Gl. = glucose; ML = M/6 lactate; Sa. = saline; S.B. = spinal block; Suc. = sucrose; Sul. = sodium sulfate; Rk. = reaction.

peared to have the more severe reactions, for in only two of the seven deaths was the history negative for hemolytic disease (Table IV, Cases 1 and 2).

The treatment varied greatly, although the majority of cases were treated with some form of glucose parenterally with or without saline. Alkalinization was employed in eight of the cases, and five deaths occurred in this group. Spinal block was used in one patient that recovered (Table IV, Case 9), although we used a celiac ganglion block without success in the one case. Four patients were treated with Rh-negative blood transfusion, and only one of these patients died. Resnick, 1946, reported rapid diuresis following the use of intravenous sodium sulfate, but Newton employed this same therapy without success.

Five autopsies were obtained. Darkinski, in referring to the renal lesions, states, "The cause of anuria would appear to be in the damage present in the glomerular filter. This is undoubtedly due to a nephrotoxic substance, the nature of which is not apparent or understood." Newton concluded, "There is no evidence of mechanical blockage in the tubules. Rather, a suppression of urine." We likewise feel that the renal lesions do not show mechanical blockage to be the basis for anuria and uremia. The suppression of urine must then be due to some other factor, the nature of which is not apparent to the author. The results of these cases have made us doubt the efficacy of massive glucose therapy and alkalinization.

Summary

1. Two deaths have been reported attributed to transfusion with Rh incompatible blood.

2. The details of treatment with autopsy findings have been presented.

3. Comparable cases from the literature have been reviewed and analyzed.

4. No conclusion is offered for the preferred method of therapy in transfusion reactions with uremia.

References

1. Aagaard, G. N.: Minnesota M. J. **25**: 267, 1942.
2. Beck, A., et al.: Brit. M. J. **2**: 180, 1944.
3. Bordley, J.: Arch. Int. Med. **47**: 288, 1931.
4. Burnham, L.: AM. J. OBST. & GYNEC. **42**: 389, 1941.
5. Butler, B. C., et al.: Surg., Gynec. & Obst. **78**: 610, 1944.
6. Cole, J.: AM. J. OBST. & GYNEC. **53**: 181, 1947.
7. Dardinski, V. J.: Am. J. Clin. Path. **15**: 286, 1945.
8. Diamond, L. K.: New England J. Med. **227**: 857, 1942.
9. Dockeray, G. C., and Sachs, H.: Brit. M. J. **1**: 492, 1942.
10. Falkenstein, A. P.: Ohio State M. J. **39**: 644, 1943.
11. Goldring, W., and Graef, I.: Arch. Int. Med. **58**: 825, 1936.
12. Halperin, J., et al.: AM. J. OBST. & GYNEC. **50**: 326, 1945.
13. Hammack, R. W.: Calif. & West. M. J. **61**: 135, 1944.
14. Mandelbaum, H.: Ann. Int. Med **12**: 1699, 1939.
15. Mayer, M. D., and Vogel, P.: J. Mt. Sinai Hosp. **8**: 300, 1941.
16. Mollison, P. L.: Brit. M. J. **1**: 529 and 559, 1943.
17. Newton, N. C., and Tebbutt, A. H.: Australia M. J. **30**: 109, 1943.
18. Pieri, R. J., and Schwartz, R. C.: Surg., Gynec. & Obst. **79**: 490, 1944.
19. Smith, C. E., and Haman, J. O.: Calif. & West. M. J. **41**: 157, 1934.
20. Vondeesten, H. T., and Cosgrove, S. A.: Ann. Int. Med. **7**: 105, 1933.
21. Wiener, A. S.: Arch. Path. **32**: 227, 1941.
22. Wiener, A. S., et al.: Am. J. Clin. Path. **11**: 102, 1941.
23. Wiener, A. S., and Peters, H. R.: Ann. Int. Med. **13**: 2306, 1940.
24. Young, L. E., and Kariher, D. H.: J. A. M. A. **127**: 627, 1945.

INCIDENCE OF ISOIMMUNIZATION AMONG Rh-NEGATIVE PREGNANT WOMEN IN PUERTO RICO

MERCEDES VICENTE DE TORREGROSA, PH.D., SANTURCE, PUERTO RICO
(From Presbyterian Hospital)

IT IS well known that Rh-negative women bearing Rh-positive children occasionally become immunized with the development of Rh antibodies. These antibodies in some instances affect the fetus, giving rise to the syndrome known as erythroblastosis fetalis.

There are two kinds of Rh antibodies: bivalent, known as agglutinins which cause in vitro visible clumping of Rh-positive red blood cells because agglutinins having two combining groups link two red cells together; and univalent, Rh antibodies also known as "blockers" or glutinins, need a third component for agglutination of the red cells to occur—this is known as conglutinin or X protein, and is present in serum or plasma.

Wiener[1] believes that there are two major disease syndromes: congenital hemolytic disease and icterus gravis, according to the type of Rh antibody present in the mother's serum.

Univalent antibodies or glutinins, being smaller, pass the placenta with greater freedom. If small amounts are present in the maternal serum the baby is born alive with anemia, or develops it shortly after birth. These babies are treated successfully with transfusions of Rh-negative blood. If large quantities of antibody are present the baby will develop extreme anemia, anoxemia, hydrops, and will be stillborn or die soon after birth. This group Wiener calls congenital hemolytic disease.

When the maternal serum contains agglutinins these bivalent antibodies, being larger, probably very seldom pass the placenta during pregnancy; at

TABLE I. BLOOD GROUP AND RH DETERMINATION OF 842 PREGNANT WOMEN

O	A	B	AB	TOTAL	O	A	B	AB	TOTAL
408	262	60	21	751	50	35	5	1	91

TABLE II. INCIDENCE OF ISOIMMUNIZATION TO THE RH FACTOR AMONG 91 RH-NEGATIVE PREGNANT WOMEN

	NO INFORMATION	NO ISOIMMUNIZATION		ANTI-Rh AGGLUTININS
Group O	7	Baby Rh pos. 32	Baby Rh neg. 10	Baby Rh pos. 1
Group A	7	19	9	-
Group B	2	-	2	1
Group AB	-	1	-	-
Totals	16	52	21	2

the time of birth due to trauma they may reach the fetal circulation. The agglutination of Rh-positive infant's cells causes the formation of thrombi which leads to a series of symptoms resulting from damage to many organs. These children usually die, but, if they survive, permanent damage may result such as mental deficiency and cirrhosis of the liver. The name icterus gravis is applied to this group.

In order as to determine the incidence of iso-immunization among Rh-negative women in Puerto Rico and of congenital hemolytic disease and icterus gravis in their siblings this study was undertaken.

In a series of 842 women 91, or 10.81 per cent, were found to be Rh negative (Table I). This figure is a little higher than the one previously reported by me[2] (10.06 per cent) in a study of Rh types among white Puerto Ricans; as only standard anti-Rh_0 serum was used in performing the Rh determinations reported in this work, a very small percentage of Rh-positive women belonging to types Rh′ and Rh″ may have been classified as Rh negative. The distribution of the four blood groups was as follows: 54.39 per cent, group O; 35.27 per cent, group A; 7.72 per cent, group B; and 2.61 per cent, group AB.

The bloods from the Rh-negative women were studied within seventy-two hours after delivery (in most instances within twenty-four hours) to determine whether Rh antibodies resulting from iso-immunization were present.

The mother's serum was tested with known O Rh-positive (type Rh_1Rh_2) and O Rh-negative red blood cells; the baby's cells were included in the tests if he belonged to the same blood group as the mother, or to group O.

In the agglutination tests, the Levine test tube technique was employed.[3] The search for "blockers" was attempted by performing the "blocking test" of Wiener[4] in the early cases. This was later substituted for the simpler and more sensitive "conglutination" test.[5]

We believe that if either agglutinins or blockers were present they would be detected with the techniques employed.

The bloods from the babies were studied to determine the Rh type, the hemoglobin, and whether there was an increase in the number of normoblasts from the expected normal in order to detect early symptoms of hemolytic disease. They were not allowed to nurse until we were convinced that there was no evidence of iso-immunization in the mother, because it has been shown that Rh antibodies may be found in maternal milk.

Of the 91 Rh-negative women in our series, there is no information on 16 of them (Table II). Seventy-three did not show evidence of iso-immunization, as there were no agglutinins or blockers present in their serum. Their babies were clinically well with hemoglobins over 110 per cent and no increase over the expected number of nucleated red blood cells in the peripheral blood. Only 52 out of these 73 women gave birth to Rh-positive infants, the rest of the siblings were Rh negative.

In the bloods of only two of these Rh-negative mothers bearing Rh-positive children anti-Rh agglutinins were detected. This makes an incidence of one Rh-negative woman out of every 26 becoming sensitized to the Rh factor through pregnancy. This figure is practically the same as found in the United States.

These two cases will be discussed in detail: a third case of an Rh-negative mother who gave birth to a child who died one hour later of erythroblastosis fetalis which was referred to us for blood studies by Dr. Parés will also be discussed.

Among the group of Rh-negative women showing no evidence of isoimmunization to the Rh factor by serological tests, two of them had stillborn babies; the death of one could be attributed to a severe pre-eclamptic toxemia of the mother, and the other one to positive maternal serology. The latter fetus was macerated and had congenital anomalies.

CASE 1.—L. D., a white woman with two living children, gave birth to a healthy baby girl. Mother group O Rh negative, baby group O Rh positive; weak anti-Rh agglutinins (titer 1) present in mother's serum. Baby's hemoglobin when born was 120 per cent; no normoblasts were seen in blood smears; she did not develop jaundice or anemia.

CASE 2.—J. A., a group B Rh-negative woman with four living children, gave birth to a male child group B, Rh positive. The mother's serum contained strong anti-Rh agglutinins (titer 32). The baby developed slight jaundice and anemia (hemoglobin went down to 81 per cent four days after birth) but recovered without transfusion therapy.

CASE 3.—T. G., a white woman with the following obstetric history: married at 18 years of age, had three full-term, apparently normal female children from first husband; two living and well at present, one died at 6 months from meningitis.

At 22 years of age the patient married a second husband. First pregnancy terminated in a spontaneous abortion at four months after a fall. In July, 1944, she delivered a full-term male stillborn child. On May 28, 1945, she gave birth to a premature child in very poor condition which died one hour after birth. The estimated date of confinement for this pregnancy was July 6, 1945. The patient had hydramnios. Fetus was premature, of grayish-blue color; had very poor respirations, moderate edema of the face, extremities, and scrotum. Its abdomen was markedly distended and indurated, the liver apparently filling the whole abdomen. After death partial autopsy revealed an enormous liver, the right lower border reaching almost to the right iliac crest, the left lobe covering completely the spleen which was also enlarged. Blood studies revealed the mother to be group O Rh negative and the baby group O Rh positive; the mother's serum contained strong anti-Rh agglutinins as well as Rh blocking antibodies. The titer of these antibodies was not determined.

*Pathologic Report.**—

Macroscopic: The specimen consisted of the spleen, gall bladder and liver of a seven-month stillborn fetus. The spleen weighed 30 Gm. and measured 6 by 4 by 3 cm. The capsule was grayish and presented numerous whitish granulations in the surface; it was of a dark wine color. On section, the organ was chocolate colored. The splenic corpuscles and the trabeculae were visible. The liver weighed 150 Gm. and measured 9.3 by 7 by 5.5 cubic millimeters. The capsule was soft and transparent. On section the parenchyma was firm and pinkish, with a slight greenish color. The cut surfaces were homogenous, and the hepatic lobules were not well outlined. The periportal tissue looked edematous. The central portion of the organ was imperfectly fixed. The *gall bladder* was of normal appearance.

Microscopic: Spleen: the Malpighian corpuscles were not very prominent. The red pulp was congested and presented numerous areas of hemorrhage, sometimes surrounding the lymphoid follicles. The sinuses were full of small hematopoietic foci constituted by red blood cells in all stages of maturation from the erythroblastic to that of basophilic and orthochromatic normoblasts.

*Obtained through the courtesy of Dr. E. Koppish from the School of Tropical Medicine, San Juan, Puerto Rico.

Among these elements were also observed megakaryocytes dispersed along the sinuses, especially in those found below the capsule.

Liver: The portal spaces were thick, edematous, and infiltrated with numerous round cells and eosinophiles. The interstitial tissue of the liver was edematous, and contained multiple hematopoietic foci comparable to those seen in the spleen. These elements were evenly distributed throughout the hepatic tissue. Frequently the cells of Kupffer were swollen and contained phagocytized erythroblasts. Around the biliary ducts of medium and large caliber there was dense infiltration constituted by round cells and polymorphonuclears; the walls of these ducts were thickened by fibroblastic proliferation.

Gall bladder: The mucosa was practically completely autolized. The mucous membrane was thick and edematous, and also the other coats. They were all diffusely infiltrated by small foci of lymphocytes and plasma cells.

Diagnosis: Erythroblastosis fetalis; chronic cholangitis.

Conclusions

This study illustrates some points which are of interest: (1) The low incidence of iso-immunization among Rh-negative women giving birth to Rh-positive children, two out of 54 in our series. (2) The correlation between the presence of Rh antibodies in the mother's serum and the baby's clinical manifestations. Of the babies born of the Rh-negative women who became iso-immunized to the Rh factor, one was not affected at all (Case 1), mother's blood had very weak anti-Rh agglutinins. The baby in Case 2 showed very mild symptoms of icterus gravis which required no treatment. Moderately strong anti-Rh agglutinins were present in the mother's serum. Case 3 gave birth to an infant who died one hour later, showing the clinical and pathologic findings of a severe form of erythroblastosis fetalis; strong anti-Rh aglutinins, as well as blocking antibodies, were found in the mother's blood.

I wish to express my gratitude to Dr. Alexander S. Wiener of Brooklyn, New York, for his valuable criticism of this paper.

References

1. Wiener, A. S.: New York State J. Med. 46: 912, 1946.
2. Torregrosa, M. V. de: Proc. Soc. Exper. Biol. & Med. 60: 715, 1945.
3. Levine, P.: Am. J. Obst. & Gynec. 42: 165, 1941.
4. Wiener, A. S.: Proc. Soc. Exper. Biol. & Med. 56: 173, 1944.
5. Wiener, A. S.: J. Lab. & Clin. Med. 30: 662, 1945.

TOTAL HYSTERECTOMY

EQUINN WILLIAM MUNNELL, M.D., NEW YORK, N. Y.

(From the Obstetrical and Gynecological Service [Third Surgical Division] Bellevue Hospital and the Department of Obstetrics and Gynecology, New York University College of Medicine)

A GREAT deal has already been written with reference to the use of total abdominal hysterectomy as a routine procedure in the removal of the uterus for benign disease. The outstanding argument in favor of removal of the cervix at the time of hysterectomy has been that it removes the possibility of subsequent development of carcinoma of the cervical stump. Less important arguments are the removal of the cervix as a possible cause of subsequent leucorrhea or focus of infection. The chief argument against the total hysterectomy as a routine procedure has been that the operative mortality and postoperative morbidity rates are higher with total than with subtotal hysterectomy. The factor of higher mortality with the total hysterectomy is borne out by smaller series of cases in the literature, but not by the large series. On the contrary, the larger series of total hysterectomies, as a general rule, show a lower mortality rate.[9, 17, 19] With few exceptions, the recommendation has been for more extensive use of the total operation, but many authors qualify this by emphasizing the importance of the skill of the individual surgeon, the consideration of increased risk because of obesity, adhesions, and fixation of the uterus, as well as the patient's general medical condition. While these authors are hesitant to advise routine panhysterectomy for "the occasional operator," they use this procedure routinely themselves and advise it for the skilled operator as a prophylaxis against subsequent cancer changes in the residual cervical stump. Objections to total hysterectomy because of shortening of the vagina or prolapse of the vault are not considered valid, since these complications need not develop if the operation is properly performed.

I. Mortality

In an eleven-year period ending May 31, 1946, 1,798 hysterectomies were performed on the gynecologic service of Bellevue Hospital. Of this number, 1,583 were subtotal hysterectomies and 215 were total hysterectomies. Of these 215, over one-half were performed in the last three years of this eleven-year period, and 165 in the last five years of this period. During the early years of this period, most of the total hysterectomies were for carcinoma of the fundus. In recent years, however, the operation of total hysterectomy for benign cases has become increasingly frequent.

By comparison with other series presented in the literature, these 215 total hysterectomies represent a small series. They were done for both malignant and benign conditions. The operative mortality rate for the group was 2.32 per cent, a total of five deaths, as compared with an operative mortality rate of 1.76 per cent, a total of 28 deaths, for the 1,583 subtotal hysterectomies.

An analysis of these five total hysterectomy deaths reveals the fact that in none of them could death be definitely attributed to the fact that a total hysterectomy was performed rather than a subtotal. The deaths were due to causes that would complicate a subtotal operation with as much frequency as they would a total hysterectomy. Table I summarizes the deaths occurring in the total hysterectomy group.

TABLE I. SUMMARY OF THE FIVE POSTOPERATIVE DEATHS IN THE TOTAL HYSTERECTOMY GROUP

PATIENT	AGE	MEDICAL COMPLICATIONS	OPERATION PERFORMED BY	OPERATION BESIDES TOTAL HYSTERECTOMY	OPERATIVE FINDINGS	CAUSE OF DEATH
D. A.	42	None	Resident	Bilateral salpingo-oophorectomy	Endometrial polyps cervicitis	Shock paralytic ileus 4th postoperative day
B. O.	42	Diabetes	Resident	Left salpingo-oophorectomy	Fibroids tubo-ovarian abscess	Pulmonary embolus 7th postoperative day
F. R.	62	Hypertensive cardiovascular disease	Attending	Bilateral salpingo-oophorectomy	Carcinoma of ovaries	Pulmonary edema 4th postoperative day
M. H.	64	Hypertension	Attending	Bilateral salpingo-oophorectomy	Post radiation Ca of fundus	Cerebral thrombosis 7th postoperative day
E. P.	40	None	Resident	Bilateral salpingo-oophorectomy	Bilateral pyosalpinx	Pulmonary embolus 1st postoperative day

Cardiovascular accidents and pulmonary emboli occur with both types of operation. The percentage of incidence of deaths from pulmonary embolus in total hysterectomy was 0.9 per cent, as against 0.6 per cent for subtotal hysterectomy.

It would seem right to assume with a greater number of total hysterectomies being performed that the operative mortality from total hysterectomy on this service should be reduced. At the present time, however, total hysterectomy on the Bellevue service carries with it a higher mortality rate than does the subtotal.

II. Postoperative Morbidity

A. *Temperature.*—The average temperature reading of 150 total and 150 subtotal hysterectomies selected from roughly the same period of time were compared. Six temperature readings per day for the day of operation and the first seven postoperative days were averaged, but only the 6 A.M. and 6 P.M. temperatures were finally used, since these were the only temperatures taken with regularity in all cases. Statistical analysis revealed no significant difference between the two groups until the 6 P.M. temperature of the third postoperative day. It was found that from this time on through the sixth postoperative day a slight but statistically significant difference existed, the total hysterectomies running a slightly higher temperature for this period of time (Fig. 1). The fact that this slightly higher average temperature exists in the total group relatively late in the postoperative course is probably caused by a low-grade inflammatory reaction about the sutures in the vaginal vault. Although the vagina was surgically prepared pre-operatively in all cases, it is impossible to create a completely sterile field in the vaginal vault.

B. *Catheterization.*—The same 300 patients, 150 total and 150 subtotal, had their charts carefully examined for the necessity of postoperative catheterization. It was found that more patients with subtotal hysterectomies had to be catheterized than those with total hysterectomies. On the day of oper-

ation 28 per cent of the subtotal required catheterization, whereas, 22.3 per cent of the total group required catheterization. On the first postoperative day about an equal percentage of each group required catheterization. More patients in the subtotal group, 30.6 per cent, than in the total group, 27.7 per cent, had to be catheterized at some time in their postoperative course. These data are summarized in Table II.

TABLE II. PERCENTAGE OF PATIENTS REQUIRING POSTOPERATIVE CATHETERIZATION IN 150 TOTAL AND 150 SUBTOTAL HYSTERECTOMIES

TYPE OF OPERATION	PER CENT REQUIRING CATHETERIZATION AT ANY TIME	DAYS POST OPERATIVE							
		O.R.	1	2	3	4	5	6	7
Total	27.7	22.3	20.9	11.4	7.4	3.3	1.3	1.3	1.3
Subtotal	30.6	28.0	20.0	8.7	4.7	3.3	1.3	1.3	0.6

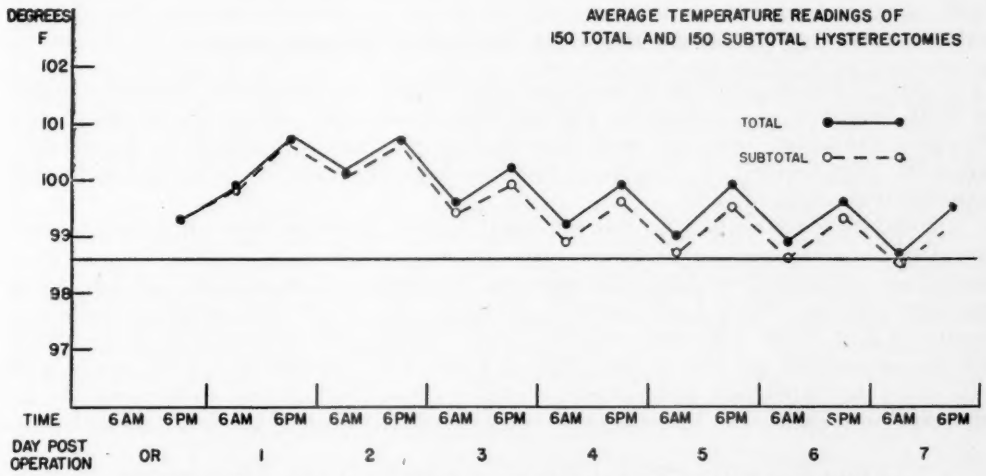

DEGREES F
AVERAGE TEMPERATURE READINGS OF
150 TOTAL AND 150 SUBTOTAL HYSTERECTOMIES
TOTAL
SUBTOTAL
102
101
100
99
98
97
TIME
6 AM 6 PM 6 AM 6 PM 6 AM 6 PM 6 AM 6 PM 6 AM 6 PM 6 AM 6 PM 6 AM 6 PM 6 AM 6 PM
DAY POST OPERATION
OR 1 2 3 4 5 6 7

Fig. 1.—Composite temperature charts of 150 total and 150 subtotal hysterectomies.

TABLE III. NUMBER OF POSTOPERATIVE PATIENTS SHOWING SLIGHT, MODERATE, OR MARKED DISTENTION IN 150 TOTAL AND 150 SUBTOTAL HYSTERECTOMIES

DAY OF OPERATION		O.R.	1	2	3	4	5	6	7
Total	Slight	2	16	23	13	1	1	1	1
	Moderate	0	6	8	5	4	2	0	0
	Marked	0	0	0	0	1	1	1	1
	Total	2	22	31	18	6	4	2	2
Subtotal	Slight	1	16	24	12	3	0	0	0
	Moderate	0	2	6	11	0	0	0	0
	Marked	0	0	0	0	2	2	2	2
	Total	1	18	30	23	5	2	2	2

C. *Distention.*—This same group of 150 total hysterectomies and 150 subtotal hysterectomies was carefully analyzed as to postoperative distention, and no significant difference found either as to the number of patients who became distended or as to the degree of distention in each group (Table III).

III. The Skill and Experience of the Surgeon

Sixty-five per cent of the total hysterectomies were performed by the resident staff.

Much has been written as to the inadvisability of the total hysterectomy being performed by the occasional operator, and most authors are in agreement that in skilled hands mortality and complications are lower. Goodall[6] advised the skilled surgeon to become as proficient in the total as in the subtotal. Ward[16] states that in average hands mortality, injuries to bladder and ureters, infection and lack of vaginal support will be higher; for himself he prefers the total operation as a prophylaxis against carcinoma of the cervical stump. Foss and Babcock[24] advise against total hysterectomy for the occasional operator. Gaston,[26] presenting a personal series, believes the total operation may be safely utilized by the general surgeon of average experience. In general, no one seems to doubt the superiority of the total hysterectomy when, as Martzloff[21] puts it, the operation is used by well-qualified individuals as an elective procedure without additional hazard to the patient. It would seem the duty, therefore, of any teaching service, turning out supposedly well-qualified gynecologic residents, to make sure its residents have become skilled in this procedure.

IV. Sexual Response Following Hysterectomy

One of the objections voiced but not written against total hysterectomies is that removal of the cervix will interfere with the sexual response of the female. However, Gaston[26] mentions that 85 per cent of his total hysterectomy patients experienced no change in their sexual life both in so far as libido and orgasm were concerned.

Sixty-five patients who led a sexual life of any activity whatsoever were carefully questioned as to frequency, desire, satisfaction (orgasm), and dyspareunia. Thirty-four had had subtotal hysterectomies and 31 had had total hysterectomies. They were further divided into those with ovarian tissue remaining and those without ovarian tissue. A general estimation of the effect of the operation on the sexual life of these two groups was then made and classified as improved, unchanged, slightly deteriorated, and deteriorated. As shown from Table IV, there was no significant difference between the subtotal

Table IV. Sexual Satisfaction and Desire Following Hysterectomy

	IMPROVED	UNCHANGED	SLIGHT DETERIORATION	DETERIORATION
Total Hysterectomy				
Both Ovaries Removed	5	7	3	4
Ovarian Tissue Remaining	4	3	3	2
Totals	9	10	6	6
Percentage	(29.0%)	(32.2%)	(19.4%)	(16.9%)
Subtotal Hysterectomy				
Both Ovaries Removed	3	8	3	4
Ovarian Tissue Remaining	6	6	2	2
Totals	9	14	5	6
Percentage	(26.5%)	(41.2%)	(14.7%)	(17.6%)

and total group, 61.2 per cent of the total group being improved or unchanged, as against 68.7 per cent of the subtotal group being improved or unchanged. It did not seem to matter whether or not ovarian tissue remained. The presence or absence of ovarian tissue did not effect the desire of either group except in the small number of patients in each group who claimed marked deterioration of sexual desire and satisfaction following operation. Fifty-three of sixty-five patients, or 81.5 per cent, after hysterectomy and of whom more than one-half no longer had ovarian tissue, claimed improvement, no change.

or only slight decrease in desire or only some delay in achieving orgasm. This should be proof enough that the deterioration in sexual response claimed by the remaining 18.5 per cent was not based on organic changes.

All but three of the patients questioned were under 50 years of age. The three patients over 50 were all total hysterectomy patients. One (aged 53 years) claimed improvement, one claimed no change (aged 52 years) and one claimed marked deterioration (aged 57 years) following total hysterectomy. Except for these three patients, the age distribution was approximately the same in both groups.

One gained three very definite impressions from careful discussion with these 65 patients. The first was that the presence of the cervix has nothing to do with the production of orgasm in the female. The same can be said about the ovary and body of the uterus. Second, a certain number of patients after hysterectomy, regardless of whether they are total or subtotal, will show some deterioration in sexual reaction. Most of these which we have classified as slightly deteriorated were patients who still had orgasm, but experienced some difficulty in reaching this point of satisfaction as quickly as they had prior to operation. Eighteen per cent of the subtotal group and 19 per cent of the total group claimed a marked deterioration. The idea of castration as being something shameful was not voiced by more than two or three of the entire 65 patients, but it was undoubtedly in the minds of many more than this. These two or three admitted it and also admitted the fact that they concealed their inability to conceive from their sexual partner or partners. The presence of the childbearing organs, regardless of whether or not they are diseased or whether or not birth control is practiced, is apparently an important factor in the sexual response of many women, and removal of these organs undoubtedly influences their sexual psyche. Most women after hysterectomy adjust themselves to this however, which brings us to the third impression, the antithesis of the second. Of those women claiming improvement of their sexual satisfaction and increase in libido, several frankly attributed it to the fact that they were no longer fearful of becoming pregnant. Many were women with children in their teens or with large families for whom each sexual act prior to operation apparently raised the subconscious fear of pregnancy, thus diminishing their desire and their satisfaction. Hysterectomy, total or subtotal, with or without remaining ovarian tissue, had rendered the sexual act a thing of pleasure alone to them.

Not only does this study deny the idea that the cervix is a necessary organ to be stimulated in order to achieve orgasm, but it also shows that neither uterus nor ovaries are necessary for its attainment. It only emphasizes the importance of the psychological factor in the female sexual response. The best example was a 45-year-old attractive, Puerto Rican woman in this series, who had two grown children and who was living with a man to whom she was not married, but for whom she cared very deeply. She was discharged from the hospital on her fourteenth postoperative day following total hysterectomy. The next day, fifteen days after total hysterectomy and bilateral salpingo-oophorectomy, she and her partner renewed their active sexual life which involved a frequency of five times a week. When seen six weeks and again three months postoperatively she stated her desire was the same as before operation and her satisfaction even greater because she no longer feared pregnancy.

Finally, then, it must be concluded that where deterioration of the sexual response occurs after hysterectomy with or without oophorectomy, this deterioration is due to the psychic trauma of the castration and not to organic changes or loss of tissue.

V. Postoperative Complications Following Total Hysterectomy

Table V presents all the complications except wound infections following 215 consecutive total hysterectomies. Comparison of the frequency of these complications with the frequency of their occurrence in subtotal hysterectomy was made in only certain of these groups. Urinary tract infection was about

TABLE V. POSTOPERATIVE COMPLICATIONS FOLLOWING TOTAL HYSTERECTOMY (BASED ON 215 CONSECUTIVE TOTAL HYSTERECTOMIES)

		NUMBER	PER CENT
Urinary tract infection		6	2.79
Intestinal obstruction		4	1.86
a. Requiring ileostomy	1		
b. Paralytic ileus	3		
Parametritis, cellulitis		3	1.39
Thrombophlebitis		3	1.39
Pneumonia		4	1.86
Cardio-vascular accident		4	1.86
a. Coronary occlusion	1		
b. Cerebral hemorrhage	1		
c. Pulmonary edema	2		
Hemorrhage from the vaginal vault		2	0.93
Pulmonary embolus with death		2	0.93
Lung infarct		1	0.40

the same in both groups. Intestinal obstruction was not compared, since in most instances in both types of hysterectomy this complication seemed dependant upon the presence of adhesions from previous operations or the character of the pelvic lesions rather than on the type of hysterectomy performed. Parametritis and cellulitis, when compared with the incidence occurring in 150 cases of subtotal hysterectomy, were found to be much less frequent in total hysterectomy, where the incidence was 1.39 per cent, as against an incidence of 6 per cent in subtotal hysterectomies. Pneumonia and cardiovascular accidents were not compared. Hemorrhage from the vaginal vault, requiring packing and transfusion, occurred twice. Pulmonary embolus with death occurred twice in these 215 total hysterectomies, an incidence of 0.93 per cent, as compared with an incidence of 0.6 per cent in 1,583 subtotal hysterectomies.

The incidence of *wound infection* was found to be slightly higher in 150 total hysterectomies than in 150 compared subtotal hysterectomies. The percentage incidence was 8.7 for the total group, as compared with 6.6 for the subtotal group.

VI. Follow-Up Complications of Total Hysterectomy

Table VI summarizes the pertinent follow-up findings after total hyster-

TABLE VI. FOLLOW-UP COMPLICATIONS OF 215 TOTAL HYSTERECTOMIES

		NUMBER	PER CENT
Granulation tissue in vaginal vault		33	15.30
Leucorrhea		9	4.13
Slight shortening of the vagina		3	1.39
Delayed healing of vaginal vault		3	1.39
Delayed induration about vaginal vault		3	1.39
Cystocele, rectocele or both		3	1.39
Vesicovaginal fistula		2	0.93
a. Carcinoma of cervix with extensive radiation	1		
b. Spontaneous healing	1		
Kinked ureter (neither re-operated)		2	0.93
Temporary rectovaginal fistula		1	0.40

ectomy. Granulation tissue in the vaginal vault on the first postoperative visit is very commonly seen, and usually disappears after about six weeks. Specific leucorrhea, usually trichomonas in type, cannot be considered related to the type of operation. Slight shortening of the vagina, one of the frequently voiced objections to the total operation, occurred in only three instances, and it should be emphasized that this shortening in all three instances was only slight. Delayed healing of the vaginal vault and delayed induration about the vaginal vault were temporary findings only. Relaxation of the vaginal walls but not of the vault appeared in three cases; incidentally, McKinnon and Counsellor[19] in a series of patients operated on for vaginal prolapse found only one case of vaginal prolapse following total hysterectomy, whereas 23 cases had a prolapsed cervical stump. One of the two cases of vesicovaginal fistula occurred following extensive radiation for carcinoma of the cervix, and cannot be rightly attributed to the fact that a total hysterectomy had been performed. The other case of vesicovaginal fistula, which also had a kinked ureter and hydronephrosis, was most certainly due to the fact that a total hysterectomy had been performed. This particular operation was performed by a resident, and the technique utilized differed from the usual technique* of the service in that clamps were used along the paracervical tissue and the bloody angles, which possibly caused the kinking of the ureter when too much tissue was incorporated in the suture. This patient was readmitted to the hospital and, while under observation, fortunately had spontaneous healing and cure. The temporary rectovaginal fistula, an accident which occurred once, was the result of an accidental laceration of the rectum at the time of operation; this patient had chronic salpingitis with a tuboovarian abscess firmly adherent to the uterus, sigmoid, and rectum; had a subtotal hysterectomy been performed, an abdominal or cervical fecal fistula surely would have developed.

VII. The Argument: Total Versus Subtotal

Table VII shows the incidence of purely benign but rather annoying subsequent symptoms and disease found in 150 cases of supracervical hysterectomy. Six per cent developed a cervicitis that was not present prior to operation. There was profuse and troublesome bleeding from the cervical canal in 2.66 per cent of cases. These follow-up complications are annoying, but certainly not serious. By the same token postoperative hemorrhage from the

TABLE VII. FOLLOW-UP COMPLICATIONS OF 150 SUBTOTAL HYSTERECTOMIES

	NUMBER	PER CENT
Cervicitis not present preoperatively	10	6.00
Cervicitis present preoperatively	7	4.66
Specific leucorrhea	5	3.30
Profuse bleeding from cervix	4	2.66
Normal menses	3	2.00

*The technique generally followed in recent years has been to achieve exposure of the uterine vessels as far down as possible to the cervicovaginal junction by sharp dissection of the adjacent broad ligament, paracervical tissue, and bladder. The vessels are then suture ligated, clamped and cut a little below the level of the internal os and then dissected free from the cervix with scissors. Progressive downward clamping and sharp dissection with the clamps always being applied medial to the vessels and incorporating minimal amounts of tissue follow. Sutures are tied down *on* the vessel stumps rather than around them after the uppermost suture ligature has been placed. This prevents the incorporation of too much parametrial tissue in the sutures and minimizes the danger of tying off or kinking the ureters. In benign cases when the vaginal vault is incised, the final extirpating incision is carried around the vault in the angle of the fornices, thus preventing shortening of the vagina. The vaginal vault is usually closed tight with interrupted sutures. The stumps of the uterine vessels may be attached to the central or lateral aspects of the closed vault in an attempt to provide the vault with the support of the cardinal ligaments. The round ligaments and tubes are not sutured to the vault, but are inverted in a purse-string suture of the cut edges of the broad ligaments; this continuous suture is continued on as a continuous over and over suture approximating the anterior bladder flap to the peritoneum of the posterior aspect of the vaginal vault.

vaginal vault and slight shortening of the vagina, the latter avoidable if the operation is properly performed, are complications that cannot be considered important. The prevention of subsequent development of cancer of the cervical stump most certainly outweighs these complications. Does it outweigh the higher mortality of the total operation? The possibility of cancer developing in the residual stump is estimated at as high as 2 per cent by McKinnon and Counsellor[19] and at less than 1 per cent by Martzloff. Assuming that 1.5 per cent of our 1,583 subtotal hysterectomies developed cancer of the cervical stump, and assuming a 27 per cent salvage rate (see Behney),[12] this would add 17 preventable deaths to the subtotal group, thus bringing the subtotal mortality to 2.8 per cent. Assuming that 1 per cent of the 1,583 cases developed cancer of the stump, and assuming as high a salvage rate as 40 per cent, this would still make enough preventable deaths to bring the subtotal rate slightly in excess of our total hysterectomy mortality rate. This is certainly not an argument for *routine* panhysterectomy in average hands; however, it should be regarded as an argument for panhysterectomy in benign cases where this operation can be performed without subjecting the patient to additional danger because of difficulty encountered in performing the total hysterectomy. Cancer of the cervix can develop in a nulliparous cervix that at one time was a clean cervix. Conversely, most cervices with cervicitis, lacerations, and erosions never develop cancer. *Would it not be better, therefore, if the decision to perform a total or a subtotal hysterectomy with a proved benign cervix be dependent more on the factor of ease of operation rather than on whether or not the cervix is clean.* Admittedly, more consideration should be given the total hysterectomy in the presence of cervicitis, but why leave in a clean but useless cervical stump if it is just as easy to remove it?

There should be no need to emphasize the importance of adequate preoperative examination of the cervix with biopsy of suspicious lesions and ideally of all lesions of the cervix. As a case in point one of the total hysterectomies in this series was done for bilateral parovarian cysts and for what was thought to be chronic cervicitis; pathologic examination of the removed uterus, however, revealed a very early League of Nations Stage I carcinoma of the cervix.

Summary

1. The mortality rate for total hysterectomy is higher than for subtotal hysterectomy in this series of 215 total hysterectomies. However, larger series in the literature, undoubtedly with selection of cases, show a higher mortality for the subtotal procedure. Increased skill from doing more and more total hysterectomies as well as proper selection of cases should reduce the mortality from total hysterectomy. Proper selection of cases involves the *ease with which the operation may be performed,* the skill of the operator, the patient's general condition, the degree of fixation of the uterus, adhesions, obesity, etc. Increased mortality is the only valid objection to the procedure and even this is not a tenable argument when the number of deaths from the possibility of cancer developing in the residual cervical stump are taken into account. *The prevention of cancer of the cervical stump is an adequate reason for performing total hysterectomy in benign cases as long as the operation does not introduce an element of extra danger to the patient.*

2. In so far as postoperative reaction is concerned, patients having had total hysterectomies will run a slightly higher temperature for a longer period

of time. Catheterization is slightly less frequent in total hysterectomies than in subtotals. Postoperative distention is approximately the same in each group.

3. The only postoperative complication that can be considered a valid objection is the possibility of injury to the bladder and/or ureters; proper technique should avoid this complication as well as that of prolapse or shortening of the vaginal vault.

4. Sexual response in women following hysterectomy is not significantly different with the cervical stump remaining than with the cervix removed. Indeed, the cervix, uterus, and ovaries seem to have little to do with libido or sexual satisfaction. Where there are changes in libido or sexual satisfaction following hysterectomy, the cause of these changes is undoubtedly psychogenic.

5. Any teaching service should consider it its duty to turn out gynecologic residents skilled in performing a total hysterectomy.

The author wishes to thank Dr. Howard C. Taylor, Jr., for his suggestions in the preparation and presentation of this study.

References

1. Farrar, L. K. P.: Surg., Gynec. & Obst. **60**: 827, 1935.
2. Healy, W. P., and Arneson, A. N.: Am. J. Obst. & Gynec. **29**: 370, 1935.
3. Richardson, E. H.: Am. J. Obst. & Gynec. **32**: 641, 1936.
3a. Richardson, E. H.: Surg., Gynec. & Obst. **48**: 248, 1929.
4. Meigs, J. V.: Am. J. Obst. & Gynec. **31**: 358, 1936.
5. Marx, Catchpole, and McKinnon, D. A., Jr.: Surg., Gynec. & Obst. **63**: 170, 1936.
6. Goodall, J. R.: Am. J. Obst. & Gynec. **32**: 628, 1936.
7. Schiller, W.: Surg., Gynec. & Obst. **66**: 129, 1938.
8. Black, M. E.: Surg., Gynec. & Obst. **68**: 898, 1939.
9. Nelson, H. M., and Weisberg, H.: Am. J. Surg. **46**: 348, 1939.
10. Farrar, L. K. P.: Trans. Am. Gynec. Soc. **64**: 248, 1940.
11. Masson, J. G.: Am. J. Surg. **48**: 255, 1940.
12. Behney, C. A.: Am. J. Obst. & Gynec. **40**: 780, 1940.
13. Smith, P. H.: Am. J. Obst. & Gynec. **40**: 118, 1940.
14. Ashton, D. L.: Am. J. Obst. & Gynec. **40**: 123, 1940.
15. Phillips, J. R., and Sears, E.: Am. J. Surg. **53**: 117, 1941.
16. Ward, G. G.: Am. J. Obst. & Gynec. **41**: 660, 1941.
17. Weir, W. C.: Am. J. Obst. & Gynec. **42**: 285, 1941.
18. Danforth, W. C.: Am. J. Obst. & Gynec. **42**: 587, 1941.
19. McKinnon, D. A., Jr., and Counsellor, V. S.: Surg., Gynec. & Obst. **74**: 957, 1942.
20. Counsellor, V. S., and McKinnon, D. A., Jr.: Surg., Gynec. & Obst. **75**: 114, 1942.
21. Martzloff, K. H.: Surg., Gynec. & Obst. **75**: 628, 1942.
22. Vogt, W. H., Jr., and Hamilton, E. G.: Am. J. Obst. & Gynec. **44**: 723, 1942.
23. Miller, H. E., and Prejean, O.: Am. J. Obst. & Gynec. **42**: 580, 1941.
24. Foss, H. L., and Babcock, J. R.: Surg., Gynec. & Obst. **76**: 214, 1943.
25. Jones, H. O., and Doyle, W. L., Jr.: Am. J. Obst. & Gynec. **46**: 160, 1943.
26. Gaston, E. A.: Surg., Gynec. & Obst. **80**: 539, 1945.
27. Foss, H. L.: Ann. Surg. **121**: 680, 1945.
28. Mengert, W. F., and Stolz, R.: Am. J. Obst. & Gynec. **49**: 603, 1945.

A COMPARISON OF THE EFFECTS OF COMMERCIAL AQUEOUS CORPUS LUTEUM SOLUTIONS AND THE PRESERVATIVE, CHLOROBUTANOL, ON UTERINE MOTILITY IN THE RABBIT*

GARDNER M. RILEY, PH.D., ANN ARBOR, MICH.

(Department of Obstetrics and Gynecology, University of Michigan Medical School)

SINCE the isolation of progesterone in the pure state in 1934,[1-3] it has been amply confirmed that this hormone of the corpus luteum is capable of exerting the physiologic effects previously obtained with crude corpus luteum extracts, notably those effects reported by Corner and Allen[4] and Hisaw and associates.[5] Progesterone, in addition to its progestational effects on the endometrium, has been shown to inhibit uterine contractions[6] and to inhibit the response of the uterus to posterior pituitary oxytocic substance. While in the human there appears little doubt that progesterone is able to modify the pattern of uterine motility, the extent to which this hormone can reduce myometrial response to posterior pituitary extracts remains controversial. The recent findings of Henry and Browne[7] showing a uterine response to pituitrin throughout the entire human menstrual cycle is in striking contrast to the common clinical observation of the noneffectiveness of posterior pituitary extracts, except during the relatively late stages of pregnancy.

The results of other studies, both previous to and following the isolation of progesterone, have suggested that some other corpus luteum factor may be capable of modifying uterine activity. Robson and Illingworth[8] prepared two corpus luteum extracts, one of which had a marked inhibitory action on uterine contractions and only a weak progestational activity; the other produced marked progestational effects but failed to inhibit the response of the uterus to pituitrin when tested in vitro. Fevold and Hisaw[9] also obtained two fractions with different activities with respect to effects on the endometrium and the response of the uterus to pituitrin. Hisaw[10] has used the kymographic tracings obtained by Foster to illustrate a difference in effectiveness of a crude corporin preparation as compared with a purified corporin extract. The former induced both a strong progestational reaction and a refractoriness of the uterus to pituitrin. The latter caused a comparable degree of endometrial change, but the uterus remained responsive to pituitrin. These early observations are of more than historical note because they have never been adequately explained, and provoke the suspicion that some heretofore unrecognized corpus luteum factor may affect uterine motility.

More recently there are claims that certain commercial aqueous corpus luteum solutions may affect uterine activity. Macht[11] reported that an aqueous corpus luteum solution lessened the response of rabbit uteri to pituitrin, in vitro. Falls and associates,[12] using the intrauterine balloon method of Moir, found that aqueous corpus luteum solutions were effective in inhibiting the oxytocic action of pituitrin on the rabbit as well as the human uterus. Furthermore, the uterine

*This study was aided by a Faculty Research Fund grant administered by Dr. Norman F. Miller, Department of Obstetrics and Gynecology, University of Michigan Medical School.

contractions of parturient women were inhibited following the administration of these solutions. These authors also summarized the results of their experiences in the use of aqueous corpus luteum solutions in the treatment of various complications of pregnancy, particularly habitual and threatened abortion, where, presumably, excessive uterine activity might be an etiologic or undesirable factor. The percentage of threatened and habitual abortion cases carried successfully to viability appeared to be significantly above that for corresponding control groups. These striking results were particularly remarkable in view of the extreme dissimilarity between the aqueous corpus luteum solutions used and the pure steroid hormone, progesterone.

The object of the present investigation was to submit commercial aqueous corpus luteum solutions to experimental tests similar to those which have been used to determine the effects of pure progesterone on uterine motility. The need for such a study is emphasized by the paucity of published data on this subject, in spite of the not infrequent clinical utilization of these preparations.

Procedures and Methods

In vitro and in vivo methods were utilized to determine the ability of commercial aqueous corpus luteum (A. C. L.) solutions to affect the motility of the rabbit uterus.

In the in vitro studies, approximately one-half of a rabbit uterus was suspended in an oxygenated Locke-Ringer's solution maintained at a temperature of 37.5° C. The volume of the bath was 200 c.c.

For the in vivo studies of uterine motility, rabbits with exteriorized cervices were prepared essentially according to the method described by Reynolds.[13] The operative procedure was simplified to the extent that the cervices were exposed by a longitudinal incision of the vaginal sheath rather than by a complete separation of the vagina from the uterine cornua. In most cases bilateral oöphorectomy was performed at the same operation. Uterine activity was recorded by an intrauterine balloon connected with a Brodie bellows through a water and air transmitting system. In later experiments the bellows was replaced by a mercury manometer which was connected with the intrauterine balloon by a continuous water system.

The aqueous corpus luteum preparations were tested for the effect (1) of continuous daily administration on the intact uterus of normal, castrate and estrogen-treated castrate rabbits; (2) of single intravenous injections on the uterine motility of unanesthetized, castrate rabbits receiving adequate estrogen to insure uterine motility; and (3) on excised uterine segments.

Tests were made of the response of the uterus and uterine strips to pituitrin or pitocin subsequent to daily treatment with A.C.L. solutions, following the addition of the solution to the bath and following intravenous injection. In a few instances, the effect of the solutions on tetanic contractions resulting from previous treatment with pitocin was determined.

Comparable studies were made of the response of the uterus, in vitro and in vivo, to varying amounts of chlorobutanol and to an aqueous solution of soluble corpus luteum extract.*

*The author wishes to express his appreciation to Dr. E. A. Sharp of Parke, Davis & Co. for providing adequate amounts of soluble corpus luteum extract. This material made possible a comparison of the effects of the corpus luteum extractives with and without the preservative, chlorobutanol.

†Acknowledgment is made to Parke, Davis & Co. for generous supplies of Aqueous Corpus Luteum Solution, Parke, Davis; to Abbott Laboratories for supplying Aqueous Corpus Luteum Solution, Abbott, and to Hynson, Wescott, and Dunning for ampules of lutein solution.

Three commercial A.C.L. solutions† were used in this study and will be designated in the text as P.D. C.L. solution, Abb. C.L. solution and H.W.D. C.L. solution, respectively. The solutions are of similar nature in that they represent the water soluble extractives of corpus luteum tissue. In this respect they differ markedly from so-called progestin extracts which possess progestogenic activity and which are derived from lipoid extracts of corpus luteum tissue. P.D. C.L. and Abb. C.L. solutions contained 0.5 per cent chlorobutanol as preservative, while H.W.D. C.L. solution contained 0.3 per cent cresol and 0.25 per cent chlorobutanol as preservatives. The manufacturers of P.D. C.L. and Abb. C.L. solutions indicate that these preparations possess no progestogenic activity. Information provided by the manufacturers of P.D. C.L. solution indicate that 18 mg. of the soluble corpus luteum extract used in this study were equivalent to the extractive contained in 1 c.c. of P.D. C.L. solution. The chlorobutanol was prepared and used as 0.5 per cent or 0.25 per cent aqueous solutions.

Effect of Daily Administration of A.C.L. Solutions on Uterine Motility

In these tests of the effects on uterine motility of continuous treatment with A.C.L. solutions, three types of rabbits were used. Three rabbits were oöphorectomized animals and received 10 R.U. of alpha estradiol daily throughout the experimental period; one was a normal, estrous rabbit, while another was an oöphorectomized rabbit which had received 60 R.U. of estrogen daily for five days previous to the initiation of treatment with A.C.L. solution. Records of uterine motility were made previous to and following treatment with the solutions. Uterine response to pituitrin was also recorded. The results of these experiments are summarized in Table I.

TABLE I. EFFECT OF DAILY TREATMENT WITH AQUEOUS CORPUS LUTEUM SOLUTION ON UTERINE ACTIVITY.

RABBIT NO.	TYPE OF ANIMAL	DAILY ESTROGEN (R.U.)	CORPUS LUTEUM SOLUTION USED		REMARKS ON CONTRACTIONS FOLLOWING TREATMENT	RESPONSE TO PITUITRIN	
			TOTAL AMOUNT (C.C.)	DURATION (DAYS)		AMOUNT (C.C.)	RESPONSE
4	Castrate*	None	12 P.D. C.L.	4	Increased amplitude, frequency unchanged	0.1	+
7	Castrate	10	30 Abb. C.L.	8	Reduced frequency	0.1	+
8	Normal	None	21 H.W.D. C.L.	7	Unchanged	0.1	+
9	Castrate	10	30 H.W.D. C.L.	10	Reduced amplitude	0.02	+
10	Castrate	10	21 Abb. C.L.	7	Greater amplitude	0.02	–

*This animal had received 60 R.U. of alpha estradiol daily for five days previous to treatment with A.C.L. solution.

When the uterine activity at the end of the treatment periods was compared with the records of motility obtained previous to treatment, little change was observed. In three instances the amplitude was modified (Fig. 1), but in no constant direction. In rabbit No. 7 the rate of contractions was reduced slightly, while in No. 8 there was no noticeable change. In all but one instance there was a marked response to pituitrin (Fig. 1). Rabbit No. 10, which had previously shown a good response to 0.02 c.c. of pituitrin, failed to give any response to the same dosage following treatment.

It is of particular interest to compare the effects of daily treatment with A.C.L. solutions with those of daily progesterone treatment. Fig. 2 illustrates

the characteristic effect of progesterone in the rabbit. In this case, after four days' treatment with progesterone, uterine motility was virtually absent, and the uterus was nonresponsive to pituitrin. As reported earlier by Reynolds,[14] a marked reduction in amplitude and frequency of uterine contractions usually occurs within one to two hours following subcutaneous injection of adequate amounts of progesterone in oil solution.

Effect of Single Intravenous Injections of A.C.L. Solutions on Uterine Motility

Ten rabbits prepared with cervical fistulas were used to test the effect of single intravenous injections upon uterine motility. After insertion of the balloon a control record of uterine activity was taken for fifteen to twenty

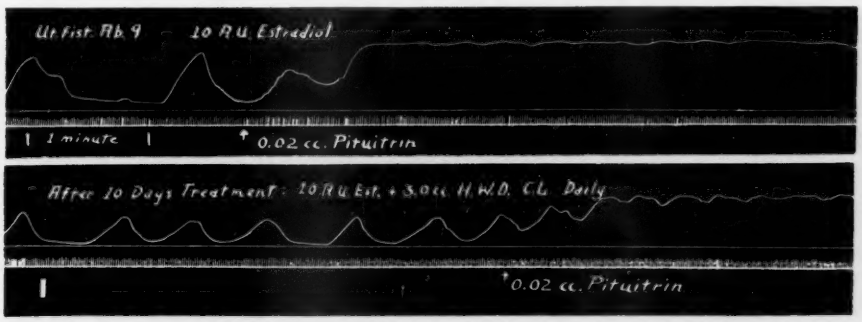


Fig. 1.—Kymographic tracings of uterine motility and response to pituitrin before treatment (upper tracing) and after ten days' treatment with a total of 30 c.c. of H.W.D. C.L. solution. The motility patterns differ but the response to pituitrin is approximately the same. The donor had received 10 R.U. of alpha estradiol daily during the experiment.

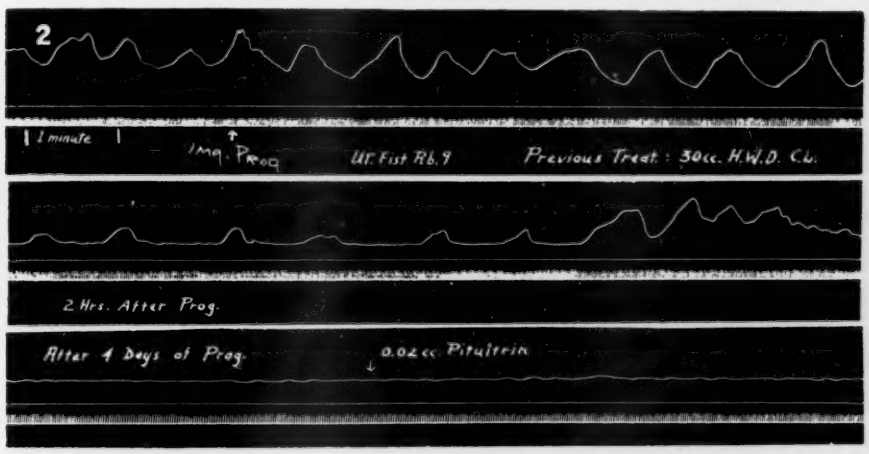


Fig. 2.—Tracings of uterine motility following progesterone treatment. This rabbit (No. 9) had previously been used to test the effectiveness of daily treatment with A.C.L. solution (see Fig. 1). Injection of 1 mg. of progesterone in oil, subcutaneously, resulted in a marked reduction in amplitude and frequency of the contractions (middle tracing). Administration of 0.25 mg. of progesterone daily for three successive days resulted in loss of contractility and refractoriness to pituitrin.

minutes. Usually a fairly regular pattern of motility was established within this period of time characterized by uniformity of successive contractions with respect to amplitude, frequency, and tonus. With two exceptions, all animals had been oöphorectomized at the time the fistula was prepared, and received daily estrogen treatment to insure uterine motility. In most instances the

TABLE II. EFFECT OF SINGLE INTRAVENOUS INJECTIONS OF AQUEOUS CORPUS LUTEUM SOLUTION ON UTERINE ACTIVITY

RABBIT NO.	DATE OF TEST	DAILY ESTROGEN (R.U.)	A. C. L. SOLUTION USED		EFFECT ON CONTRACTIONS
			SOLUTION	AMOUNT C.C.	
2 N*	4/19	–	P.D. C.L.	2	Increased regularity only
	4/23	–	P.D. C.L.	4	Reduced amplitude and frequency
4 C†	5/21	60	P.D. C.L.	4	Progressive reduction in amplitude and frequency to inactivity
5 C	8/3	60	P.D. C.L.	4	Reduced frequency
	8/5	60	P.D. C.L.	3	None
	8/26	60	P.D. C.L.	3	Reduced amplitude
	9/17	60	P.D. C.L.	3	None
6 C	8/14	5	H.W.D. C.L.	3	Marked reduction in tonus
	8/17	5	H.W.D. C.L.	3	Reduced tonus
	8/20	5	H.W.D. C.L.	3	Reduced tonus
7 C	9/7	10	H.W.D. C.L.	3	Reduced amplitude
	9/9	10	H.W.D. C.L.	3	Reduced tonus
	9/10	10	H.W.D. C.L.	3	Reduced tonus and frequency
	9/13	10	H.W.D. C.L.	3	Reduced frequency
	9/14	10	H.W.D. C.L.	3	Reduced tonus and frequency
	9/17	10	H.W.D. C.L.	3	None
8 N	8/31	–	H.W.D. C.L.	3	Marked reduction in tonus
9 C	9/17	10	H.W.D. C.L.	3	None
	9/30	10	H.W.D. C.L.	3	Reduced tonus
10 C	10/5	10	Abb. C.L.	3	Marked reduction in tonus and amplitude
	10/6	10	Abb. C.L.	3	Slight loss of tonus, reduced amplitude
11 C	10/12	5	Abb. C.L.	3	Gradual reduction in tonus
	10/14	5	Abb. C.L.	3	Progressive reduction in tonus, amplitude and frequency
14 C	7/31	10	Abb. C.L.	3	None

*N indicates a normal estrous rabbit.
†C indicates a bilaterally oöphorectomized rabbit.

single injection consisted of 3 c.c. of A.C.L. solution. The amounts of the different solutions used, the amount of estrogen administered daily, and the effect on contractions are tabulated in Table II.

There was considerable variation, both qualitatively and quantitatively, in the effect of the injections upon the established motility pattern. This variation obtained for different animals as well as for different tests on the same animal. In every instance where an effect was noted (78.2 per cent of the tests), the change was toward a less active uterine motility. This change was characterized in some instances by a marked reduction in tonus as well as decreased amplitude and rate of contraction (Fig. 3). In other instances only regularity, frequency, or amplitude was affected. In five tests there was no observable effect upon contractions. The absence of effect is interesting, since in three animals (Nos. 5, 7, and 9) striking effects were obtained in other trials.

A few similar tests were made using either chlorobutanol or soluble corpus luteum extract. The tests with chlorobutanol consisted of injections of 3 c.c. of a 0.5 per cent solution. The soluble corpus luteum extract was dissolved in distilled water in concentrations of 18 mg. to 1 c.c. Three to six c.c. of this solution were used for the several tests.

The motility was reduced or tonus lowered in four of eight trials with chlorobutanol. In four tests with soluble corpus luteum extract there was no effect on uterine motility.

Effect of Soluble Corpus Luteum Extract on Response of Uterus to Pituitrin

Using three rabbits, comparisons were made between the response of the uterus to 0.5 U. of pituitrin and to 0.5 U. of pituitrin plus 108 mg. of soluble

corpus luteum extract (equivalent to the amount of this extract in six 1 c.c. ampules of P.D. C.L. solution). The intervals between administration of pituitrin and the extract were 1.0, 1.5, 4.0, and 4.5 minutes in four tests.

Fig. 4 illustrates the failure of this amount of extract to modify the characteristic recovery from the effects of the oxytocic agent.

Effect of A.C.L. Solutions on Uterine Strips

Table III summarizes the effects of commercial A.C.L. solutions, Soluble Luteum extract, and chlorobutanol on the contractility of uterine strips. Reduced motility or lowered tonus followed the addition of both A.C.L. solutions and chlorobutanol in a majority of instances.

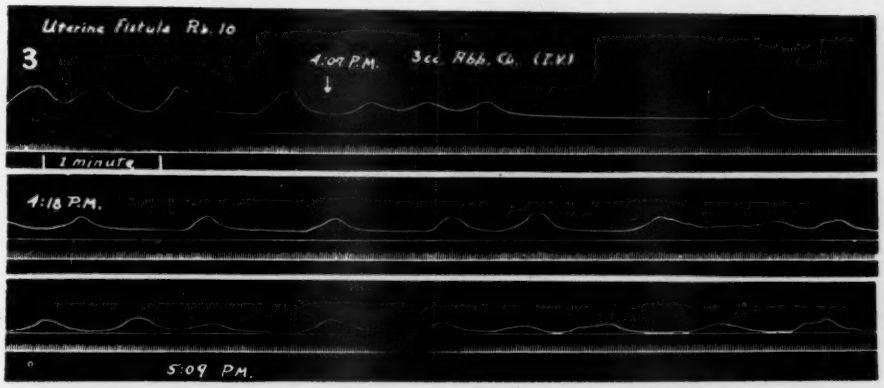


Fig. 3.—Effect of a single intravenous injection of 3 c.c. of Abb. C.L. solution. A decrease in tonus, amplitude and rate of contractions rapidly followed this treatment.

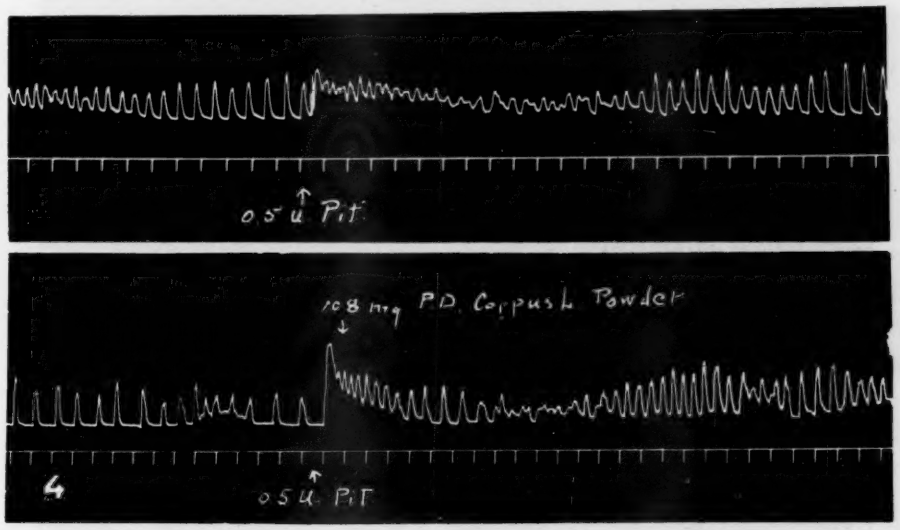
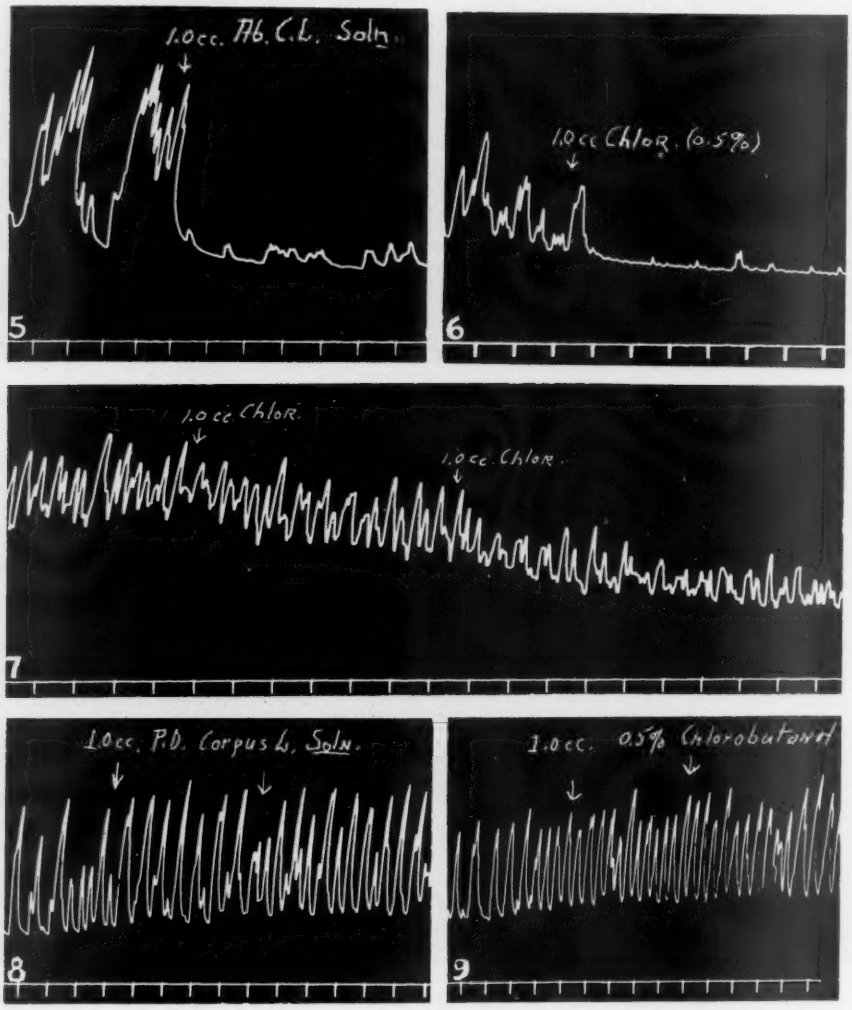


Fig. 4.—Tracings comparing the recovery from the oxytocic effects of Pituitrin (upper tracing) and pituitrin followed by 108 mg. of soluble corpus luteum extract (equivalent to the corpus luteum extractives in 6 c.c. of P.D. C.L. solution). The recovery patterns are very similar. Time in minutes is recorded on the base line.

The addition of 1 c.c. of A.C.L. solution modified uterine motility in 78.9 per cent of the trials while the addition of the same amount of 0.5 per cent chlorobutanol had comparable effects in 86.4 per cent of the tests. Both solutions

were effective in reducing the activity of uteri from castrated and estrogen-treated donors as well as uteri from donors which had been pseudopregnant from two to five days.

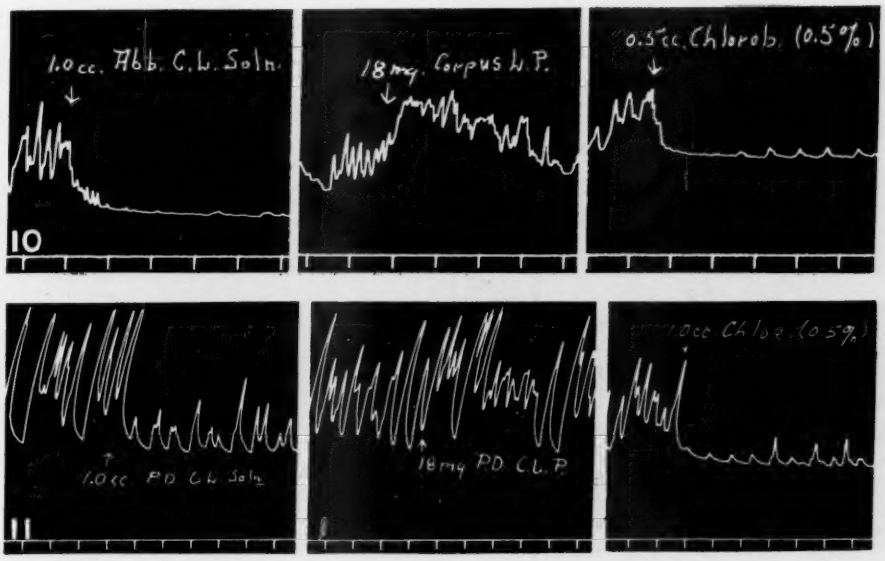
The degree of response to these preparations varied considerably. The most striking and characteristic effect was a reduction in amplitude and frequency of the contractions (Figs. 5 and 6). In numerous tests activity virtually ceased. Frequently reduced activity was associated with a reduction in tonus. In some instances a relative refractoriness to the solutions was exhibited (Fig. 7). In such cases more marked inhibition was attained by increasing the concentration of the solution. Occasionally the uterine strip appeared virtually unaffected (Figs. 8 and 9). It is notable that strips showing relative or complete refractoriness to an A.C.L. solution invariably exhibited a comparable refractoriness



Figs. 5-9.—Kymographic tracings showing several grades of response of uterine strips to A.C.L. solutions and chlorobutanol. Figs. 5 and 6.—Maximal inhibition of contractility following Abb. C.L. solution and chlorobutanol demonstrated on the same uterine strip. The bath was changed between recordings. Fig. 7.—Intermediate grade response to chlorobutanol. Note the progressive decrease in tonus and amplitude with increasing concentration of chlorobutanol. Figs. 8 and 9.—Two tracings obtained from the same uterine strip showing a total refractoriness to both P.D. C.L. solution and chlorobutanol. Bath changed between recordings. Time in minutes is recorded on the base line.

to chlorobutanol. Regardless of the degree of reduced activity, the uterine muscle responded to pitocin or pituitrin.

Soluble corpus luteum extract administered as an aqueous solution failed in every instance to reduce activity. On the other hand, the addition of this extract invariably resulted in increased tonus or activity. Figs. 10 and 11 illustrate the responses of two uterine strips to the three different preparations.



Figs. 10 and 11.—Tracings obtained from two uterine strips comparing the effectiveness of A.C.L. solutions, soluble corpus luteum extract, and chlorobutanol in reducing contractile activity. Fig. 10.—Sections of three tracings on the same uterine strip. The bath was changed between recordings. Abb. C.L. solution and chlorobutanol reduced motility whereas 18 mg. soluble corpus luteum extract (indicated as Corpus L.P. in figure) had a pronounced stimulatory effect. Fig. 11.—Sections from three tracings on another uterine strip. P.D. C.L. solution and chlorobutanol reduced activity while 18 mg. of soluble corpus luteum extract (indicated as P.D. C.L.P. in figure) temporarily increased tonus. Time recorded in minutes on base line.

Discussion

The germicidal and antiseptic properties of chlorobutanol (chloretone) have resulted in its common use as an effective preservative of numerous pharmaceutical preparations. In some of these preparations, such as extracts of the posterior pituitary, the active hormonal agent has a high degree of pharmacological potency and is effective in relatively small quantities. In such cases it is doubltful that a small amount of preservative agent would either interfere seriously with the action of the active agent or exert any significant effect of its own. On the other hand, when a preparation such as an aqueous corpus luteum solution is administered at frequent intervals, over long periods of time with individual doses of the order of one to three c.c., it would appear important to give consideration to all the physiological and pharmacological properties of that preparation. Since aqueous corpus luteum solutions may consist of extractives dissolved in 0.25 per cent to 0.5 per cent solutions of chlorobutanol, attention must be directed to the possible effects of this solvent.

TABLE III. COMPARATIVE EFFECTIVENESS OF AQUEOUS CORPUS LUTEUM SOLUTIONS, SOLUBLE CORPUS LUTEUM EXTRACT AND CHLOROBUTANOL IN REDUCING THE CONTRACTILE ACTIVITY OF UTERINE STRIPS

MATERIAL TESTED	TYPE OF DONOR	AMOUNT OF SOLUTION OR EXTRACT (C.C.)	CONCENTRATION OF CHLOROBUTANOL (%)	NUMBER OF TESTS	NUMBER SHOWING REDUCED MOTILITY	PERCENTAGE OF TESTS SHOWING REDUCED MOTILITY (PER CENT)
Aqueous corpus luteum solutions (0.5 per cent chlorobutanol as preservative)	Estrous	1.00+	0.00125	1	1	
	Estrous	1.00	0.00250	19‡	15	78.9
	Estrous	2.0	0.00500	5	2	
	Estrous	3.00	0.00750	1	1	
	Castrates receiving estrogen	1.00	0.00250	5	5	
		2.00	0.00500	3	3	
		3.00	0.00750	1	1	
	Pseudopregnant	1.00	0.00250	1	1	
		(MG.)				
Soluble corpus luteum extract (no chloro-butanol)*	Estrous	18.00		13	0	00.0
		36.00		3	0	
	Pseudopregnant	18.00		3	0	
		(C.C.)				
Chlorobutanol, 0.5 per cent	Estrous	0.50	0.00125	4	4	
		1.00	0.00250	22	19	86.4
	Castrates receiving estrogen	2.00	0.00500	4§	1	
		1.00	0.00250	2	0	
	Pseudopregnant	0.25	0.00060	3	0	
		0.50	0.00125	5	5	
		1.00	0.00250	2	2	

*18 mg. of this extract was equivalent to the amount of extractive in 1 c.c. of P.D. C.L. solution.

†The aqueous corpus luteum solution used in this test contained 0.25 per cent chlorobutanol.

‡In two trials a solution containing 0.25 per cent chlorobutanol was used.

§The uterine strips had previously failed to respond to lower concentrations.

The hypnotic and anaesthetic properties of chlorobutanol have long been recognized,[15] and its antispasmodic effect has been utilized in attempts to prevent or relieve nausea.[16] Perhaps in recognition of its antispasmodic effect, chloretone has been used with reported success in the treatment of dysmenorrhea.[17] To the author's knowledge, the only experimental study of the effect of chloretone on smooth muscle contractility is that of Terasaka.[18] This author states that chloretone in concentrations of 0.02 per cent lowered the tonus, in vitro, of excised strips of the small intestine of rabbits, and reduced the spontaneous activity of uterine strips. The report is a brief summary of observations and includes no data. The results of the present investigation not only confirm the findings of the earlier author, but indicate the effectiveness of concentrations of the order of 0.00125 to 0.0025 per cent.

While the effects of aqueous corpus luteum solutions compare very closely with those of chlorobutanol, soluble corpus luteum extract (a water soluble extract of corpus luteum tissue free of any preservative agent) either produced no change in uterine contractility or increased activity. The evidence points

strongly to the probability that the effect of the aqueous corpus luteum solutions was produced by the preservative, chlorobutanol, rather than by a specific factor of the corpus luteum extract.

The A.C.L. solutions used in this study do not possess three physiologic activities which are well established as properties of progesterone: (1) they do not induce progestational changes in the rabbit endometrium (unpublished observations of the author); (2) repeated injections do not result in uterine quiescence; (3) repeated injections do not inhibit the response of the uterus, either in vitro or in vivo, to posterior pituitary extracts.

Falls and co-workers[12] report that treatment of a postpartum subject with 10 c.c. of an aqueous corpus luteum solution, following a previous injection of pituitrin, lowers uterine tonus and slows the rate of the contractions. This type of test was not utilized to any great extent in the present investigation due to the observation that while the recovery following response to pituitrin may in general follow a typical pattern, there may be marked variations with respect both to speed of recovery and amplitude and frequency of contractions. In one experiment described above it was found that an amount of soluble corpus luteum extract equivalent to the extractive contained in 6 c.c. of one of the A.C.L. solutions did not significantly modify recovery from the tetanic contractions induced by pituitrin. In the author's judgment, this type of test cannot be applied satisfactorily to true progestogenic preparations. The progestogenic agent, dissolved in an oil medium, is administered parenterally and a latent period occurs before effective amounts of the hormone can be absorbed. During this interval some degree of recovery from the oxytocic stimulus might be expected which would be unrelated to the injected progestogenic substance.

Macht[11] concluded that a uterine strip from a rabbit pretreated with an aqueous corpus luteum solution is less sensitive to pituitrin than a strip from the same animal before such treatment. The present experiments do not disclose whether or not the degree of sensitivity to this drug is altered. They do, however, emphasize that uteri of rabbits treated with these solutions do continue to respond to the oxytocic factor of the posterior pituitary.

The above described results indicate a striking inhibitory effect of chlorobutanol on uterine contractions and emphasize the possibility of this factor exerting a pharmacological effect when these solutions are used clinically or experimentally.

The variations in responsiveness to chlorobutanol have not been explained. In general, the greater the initial spontaneous contractile activity of a uterine strip, the less it was affected by chlorobutanol (compare Figs. 5 and 9). This suggests that some unrecognized physiologic condition of the donor modifies the response of the uterine muscle to the pharmacological agent. The comparative studies on uteri from estrous and pseudopregnant rabbits did not contribute to an elucidation of this problem since uteri from the latter type of animals showed the same variability in responsiveness.

Summary and Conclusions

1. In vitro and in vivo methods were used to test the effect of three commercial aqueous corpus luteum (A.C.L.) solutions, a soluble corpus luteum extract, and the preservative agent, chlorobutanol, on uterine motility in the rabbit.

2. Daily treatment with commercial A.C.L. solutions for four to ten days had no significant effect upon uterine motility, in vivo. A characteristic uterine response to pituitrin was obtained in all but one instance.

3. Single intravenous injections of commercial A.C.L. solutions had varying degrees of effect on uterine motility. In approximately three-fourths of the tests, the effect was in the direction of reduced motility. The effect of chlorobutanol was equally variable but in the same direction. Aqueous solutions of a soluble corpus luteum extract were without effect.

4. In a majority of instances commercial A.C.L. solutions and chlorobutanol reduced the motility of uterine strips. The addition of these preparations to the bath did not interfere with the response of the muscle to oxytocic agents.

5. These studies clearly indicate that the three commercial aqueous corpus luteum solutions tested possess a property capable, under the conditions of the aforedescribed experiments, of reducing uterine activity. These preparations contained, as a preservative agent, 0.25 or 0.5 per cent chlorobutanol. It was demonstrated that chlorobutanol itself is capable of reducing the motility of uterine muscle. On the other hand, an aqueous solution of a soluble corpus luteum extract, claimed to be a component of one of the commercial solutions, did not reduce uterine activity. In view of these findings the possibility is suggested that some reports of the effectiveness of commericial aqueous corpus luteum solutions in reducing uterine activity may be due to the chlorobutanol factor rather than to some heretofore unrecognized property of the corpus luteum.

References

1. Slotta, K. H., Ruschig, H., and Fels, E.: Ber. d. deutsch. chem. Gesellsch. **67**: 1270, 1934.
2. Butenandt, A., and Westphal, U.: Ber. d. deutsch. chem. Gesellsch. **67**: 1440, 1934.
3. Allen, W. M., and Wintersteiner, O.: Science **80**: 190, 1934.
4. Corner, G. W., and Allen, W. M.: Am. J. Physiol. **88**: 326, 1929.
5. Hisaw, F. L., Fevold, H. L., and Meyer, R. K.: Physiol. Zoöl. **3**: 135, 1930.
6. Allen, W. M.: Am. J. Physiol. **92**: 174, 1930.
7. Henry, J. S., and Browne, J. S. L.: Am. J. Obst. & Gynec. **45**: 927, 1943.
8. Robson, J. M., and Illingworth, R. E.: Quart. J Exper. Physiol. **21**: 93, 1931.
9. Fevold, H. L., and Hisaw, F. L.: Proc. Soc. Exper. Biol. & Med. **29**: 620, 1932.
10. Hisaw, F. L.: In Sex and Internal Secretions, ed. 1, Baltimore, 1932, Williams & Wilkins Co., Chap. XI.
11. Macht, D. I.: Surg., Gynec. & Obst. **66**: 732, 1938.
12. Falls, F. H., Rezek, G. H., and Benensohn, S. J.: Surg., Gynec. & Obst. **75**: 289, 1942.
13. Reynolds, S. R. M.: Am. J. Physiol. **92**: 420, 1930.
14. Allen, W. M., and Reynolds, S. R. M.: Am. J. Obst. & Gynec. **30**: 309, 1935.
15. Houghton, E. M., and Aldrich, T. B.: J. A. M. A. **33**: 777, 1899.
16. Ellerson, E. M.: Virginia M. Monthly **67**: 755, 1940.
17. Wynter, W. E.: The Lancet **2**: 1245, 1929.
18. Terasaka, M.: J. Chosen Med. A. **85**: 168, 1928.

EPISIOTOMY BLOOD LOSS

LESTER D. ODELL, M.D., AND ARTHUR SESKI, M.D., CHICAGO, ILL.
(From the Department of Obstetrics and Gynecology of the University of Chicago and the Chicago Lying-In Hospital)

MANY methods are described for measuring blood loss in obstetric patients. But, basically, these are four: Williams[1] measured blood caught in basins. Schmid[2] weighed bloodstained linen before and after washing and drying, the difference representing grams of blood lost. Pastore[3] expressed blood loss as percentage body weight computed from changes in the cell volume during the puerperium. Dieckmann and Daily,[4] using a modification of Gatch and Littles' method,[5] converted blood and linen washings to acid hematin with 0.1 N hydrochloric acid, and calculated blood loss by formula. Inaccuracies from amniotic fluid, particularly the "after waters," makes the first two methods of less certain value. Coller and associates[6] and Dieckmann and Daily doubt if a sound correlation exists among changes in hematocrit, hemoglobin, and plasma proteins before and after blood loss. The fourth method, then, is apparently the best.

Few reports exist concerning episiotomy blood loss. Conn and co-workers,[7] using a modification of Williams' method,[1] reported average total blood loss for primiparas with episiotomy as 397 ml. and 189 ml. without, the calculated difference being 208 ml. Dieckmann and Daily[4] employed the acid hematin method on fifteen patients and found an average total blood loss (episiotomy plus uterine) of 342.3 ml. These same investigators noted a considerable variation in amounts of blood lost, and reasoned that a larger series would become of little additional value.

Obviously, several factors influence episiotomy blood loss, such as: the type, depth, and duration of anesthesia, parity, extent of episiotomy, traumatic delivery, presence or absence of vulvar varicosities, individual variations, and, of considerable importance, the elapsed time. It has occurred to us that most of these might be controlled in carefully selected cases; that episiotomy blood loss would relate directly to time, and therefore might be expressed as milliliters of blood lost per minute.

Material

A total of 71 patients were selected for study. One group consisted entirely of women with normal pregnancies and uncomplicated labors. In this group pelvic measurements, particularly of the outlet, were adequate. All were primigravidas and the occiput was in an anterior position, two to three centimeters below the ischial spines (low forceps) or crowning at the vulva (outlet forceps), when each experiment was performed. In a second group of patients, also consisting of primigravidas, some complicated deliveries occurred.

Method

Each collection of blood was made with the patient in a lithotomy position, with a double thickness of waxed paper beneath the hips, and with the end of this paper directed toward a floor basin containing about 1,000 ml. 0.1 N hydrochloric acid. Episiotomies, performed with scissors, were all left mediolateral in location. The operation consisted of three incisions, as described by DeLee[8]: an initial perineal incision, a second cutting intercolumnar facia and thus exposing levators, and a third incising the vaginal mucosa. Delivery was completed with forceps following the episiotomy incisions.

Three phases of episiotomy bleeding were recognized: that phase from the initial incision until the infant's head distended the vulva and controlled bleeding; phase two, consisting of that time during which the infant is delivered; and phase three, that period after delivery until completion of the episiotomy repair. Significant bleeding occurs only during the first and third phases, and blood was collected separately for these periods. Furthermore, the elapsed times for phases one, two, and three were measured, and blood loss per minute calculated for periods one and three. Oxytocics, consisting of solution of intravenous pituitary or ergotrate or both, were administered during phase two to insure rapid placental detachment. And, following an early expression of the placenta, a tail-sponge was packed against the cervix to contain any additional uterine blood.

Three groups of patients were studied during phase one: those in which no tamponade was employed; another group in which a sponge was stuffed* into the wound; and a third in which bleeding vessels were ligated prior to completion of the delivery by forceps. Ethylene-ether anesthesia was used for each group. Cases investigated under cyclopropane, ether, and spinal anesthesia are reported collectively under total episiotomy blood loss. Except for a few designated cases, the infant was delivered slowly following birth of the head, a method advocated by Dieckmann.[9]

The method for acid hematin extraction was as described by Dieckmann and Daily,[4] with the exception that the Coleman spectrophotometer Model 11 was used instead of the Dubosecq instrument. Blood loss was calculated by the following formula: $\text{ml blood loss} = \frac{\text{total grams hemoglobin recovered}}{\text{grams hemoglobin/100 ml. patients blood}} \times 100$.

The recovery ratio for the acid hematin method was tested as follows: Known amounts of blood were poured over four Mayo-type sponges; 1,000 ml. 0.1 N hydrochloric acid was added; the sponges were washed and wrung out by hand in that solution. In a second group the sponges were rinsed in addition in 500 ml. 0.1 N hydrochloric acid; and that solution was added to the original. In both groups the solutions were diluted to the nearest convenient mark for analysis.

Results

Table I lists the recovery ratios by the acid hematin method. In a single washing 83 to 92 per cent was recovered. But, if soiled sponges were rinsed, a consistently higher average of recovery occurred (95 to 98 per cent).

Fig. 1 illustrates total episiotomy blood loss for forty patients. Although the average loss for this group was 253 ml., the variation was considerable. These cases were drawn from the private and clinic services, and episiotomies were left mediolateral in location.

Table II lists total blood loss for the first phase by the previously defined methods. Although the average blood loss per minute was significantly reduced for those with tied vessels and stuffed sponge, *the total blood loss of this*

*Insertion of a folded Mayo-type sponge into the episiotomy wound.

TABLE I. PERCENTAGE RECOVERY OF KNOWN AMOUNTS OF BLOOD BY ACID HEMATIN METHOD

SINGLE WASHING			RINSED SPONGES*		
ML. BLOOD	ML. RECOVERED	PERCENTAGE RECOVERY	ML. BLOOD	ML. RECOVERED	PERCENTAGE RECOVERY
25	23.0	92.0	25	24.3	98.0
50	41.5	83.0	50	48.6	97.4
100	91.8	91.8	100	95.4	95.4
250	227.5	91.0	250	240.0	96.0

*Note that a higher percentage of recovery occurred if soiled sponges were rinsed, and this rinse water added to the original solution.

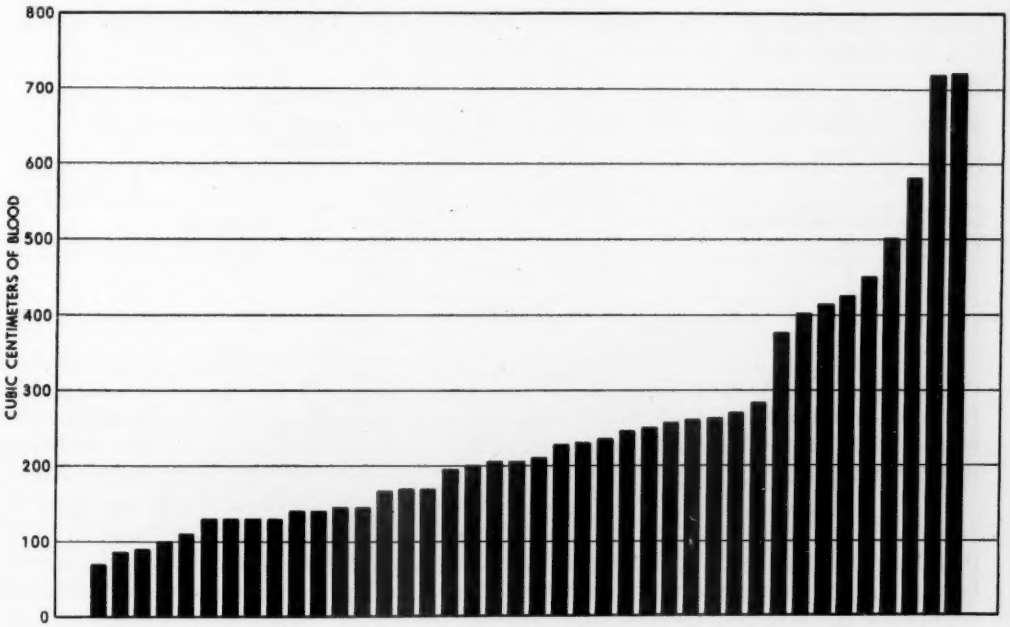


Fig. 1.—Total episiotomy blood loss in forty primigravidas.

TABLE II. BLOOD LOSS DURING FIRST PHASE

	OBSERVATIONS	VARIATION		AVERAGE ML./MIN.
		ML. BLOOD	TIME MIN. SEC.	
Low forceps, no tamponade	20	46.5 to 289	1 10 to 5 45	50.1
Stuffed sponge	8	30.1 to 322	1 to 4 30	56.7
Stuffed sponge and tied vessels	6	94.0 to 339	3 to 10 35	33.5
Thrombin with sponge	10	72.0 to 322	2 40 to 6 42	29.6
Outlet forceps, no tamponade	9	28.0 to 74	2 to 5 15	16.1

group was high. The average blood loss for outlet forceps was comparatively low, 16.1 ml. per minute; and the use of thrombin (applied with a Mayo sponge) significantly reduced bleeding. Fig. 2 illustrates graphically the linear relationship between blood loss and elapsed time during phase one.

The average time for twenty primigravidas terminated by slow delivery was three and one-fourth minutes. Seven additional patients were delivered in an average time of one and one-half minutes.

Phase three is listed for slow delivery as well as for more rapid delivery (Table III). Note the marked decrease in the total blood lost and ml. loss per minute for this period as contrasted with that measured during phase one (Table II). In addition, the average loss following slow delivery, 3.1 ml. per minute, was significantly lower than the average (4.4 ml. per minute) following the faster delivery.

TABLE III. BLOOD LOSS DURING THIRD PHASE

	OBSERVATIONS	VARIATION		AVERAGE ML./MIN.
		ML. BLOOD	TIME MIN.	
Low forceps, slow delivery	20	43.6 to 190	16 to 52	3.1
Faster delivery	7	52.5 to 110	13 to 30	4.4

Comment

The efficacy for recovery of hemoglobin by the acid hematin method is consistent. Dieckmann and Daily[4] recovered 87 to 90 per cent of hemoglobin from known quantities of blood with a single washing. And, if soiled sponges were rinsed, and this rinse water added to the original solution, the recovery was 98 per cent. The results in this report (Table I) confirm their observation.

The results of this study indicate that total episiotomy blood loss may be considerable, and probably constitutes the chief source for blood loss in most primiparous patients. The average total episiotomy loss of 253 ml. is certainly high by comparison, since the uterine blood loss following intravenous ergotrate is reported as less than 100 ml. in 81 per cent of patients,[10] and as low as 51.9 ml. following slow delivery and intravenous pituitrin and ergotrate.[9]

Stuffing a Mayo sponge into the episiotomy wound during phase one does not significantly reduce the total blood loss or decrease that lost per minute. This practice only serves as a wick to soak up the blood, and probably deludes the operator into believing that less blood is lost. Some clinicians clamp and ligate bleeding vessels. But this procedure occupies valuable time, and the total amount lost is increased even though the loss per minute is less. Since the blood lost relates directly to time consumed (Fig. 2), the amount of bleeding can be significantly reduced by shortening phase one. Episiotomy blood loss during this period can be as low as 46.5 ml. (Fig. 2).

A dramatic change occurs in the rate of episiotomy bleeding following delivery (Table III). The marked reduction in ml. lost per minute (50.1 ml. before delivery and 3.1 ml. after delivery in those without tamponade) has two probable explanations. The first concerns the effect of the infant's head and body, which acts as a tamponade during its passage through the introitus, and during which the ends of cut vessels are obliterated by pressure. The lower loss during outlet forceps supports this concept, as does the noticeably greater rate per minute following a faster delivery, when tamponade occurs for a shorter length of time. A second possibility concerns changes in venous circulation before and after delivery. Considerable venous congestion, as evidenced by protruding external hemorrhoids, promotes more bleeding prior to

delivery. Whereas immediately after delivery circulation becomes reestablished between perineal venous plexuses and pelvic veins, and this congestion becomes relieved. Thus, much less episiotomy bleeding occurs during phase three.

Thrombin, applied to the episiotomy with a Mayo-type sponge, was used on ten patients. Blood loss during phase one was reduced and bleeding from that wound after delivery was lessened.

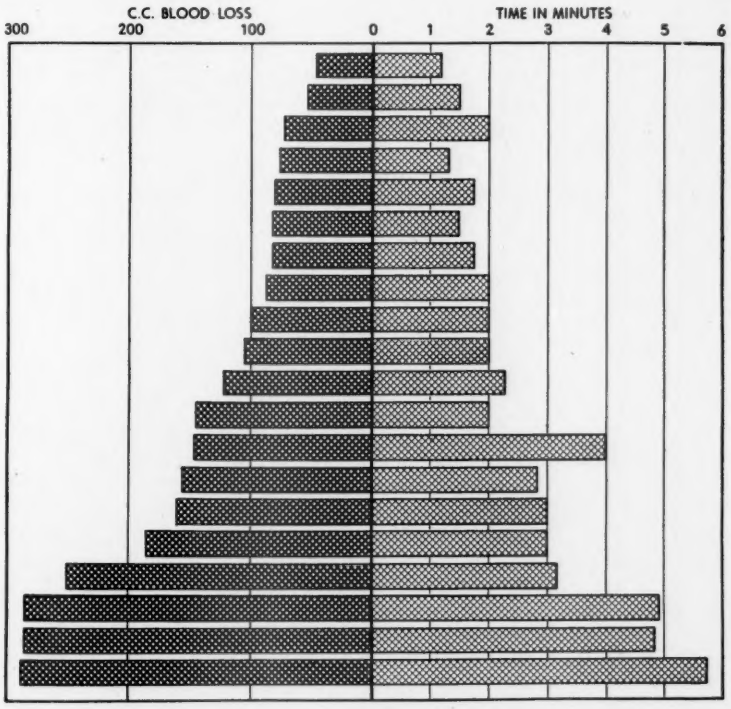


Fig. 2.—Episiotomy blood loss. Relationship between elapsed time and blood lost during first phase.

Summary

Following left medial lateral episiotomy, the amount of blood lost is directly related to time: the time consumed between the incision and the tamponade of the wound by the infant's head. And this period has been designated as phase one. The use of a stuffed sponge in episiotomy wounds does not significantly reduce blood loss per minute during phase one when compared with those cases where no tamponade is used. Ligation of bleeding vessels will reduce the blood lost per minute (during the first phase), but the total blood loss becomes increased because of the time consumed. Total blood loss during phase one can be significantly reduced by shortening the time for that period. In addition, the episiotomy blood loss per minute during outlet forceps delivery, or after the application of thrombin to the wound, is less by comparison with that during low forceps (without tamponade).

Phase two, that period of actual delivery, is without significant bleeding.

During the third phase, that period after delivery until completion of the episiotomy repair, the rate of bleeding is much less by comparison with phase one. This rate is less following slow than following more rapid delivery. The mechanism for the reduced rate of bleeding during phase three is explained.

References

1. Williams, J. W.: Am. J. Obst. 90: 1, 1919.
2. Schmid, H. H.: Halbon u. Seitz 8: Part 1, 108, Urban and Schwarzenberg, Berlin, 1927.
3. Pastore, J. B.: AM. J. OBST. & GYNEC. 32: 859, 1936.
4. Dieckmann, W. J., and Daily, E. F.: AM. J. OBST. & GYNEC. 30: 221, 1935.
5. Gatch, W., and Little, W.: J. A. M. A. 83: 1075, 1924.
6. Coller, F. A., Crook, C. E., and Job, V.: J. A. M. A. 126: 1, 1944.
7. Conn, L. C., Vant, J. R., and Cantor, M. M.: AM. J. OBST. & GYNEC. 42: 768, 1941.
8. DeLee, J. B., and Greenhill, J. P.: The Principles and Practice of Obstetrics, ed. 8., Philadelphia, 1943, W. B. Saunders Company.
9. Dieckmann, W. J., Odell, L. D., and Seski, A.: Unpublished data.
10. Davis, M. E., Boynton, M. W.: AM. J. OBST. & GYNEC. 43: 775, 1942.

FERTILITY IN WOMEN: THE LENGTH OF TIME REQUIRED TO CONCEIVE

A. W. DIDDLE, M.D., DALLAS, TEXAS, R. W. JACK, M.D., MIAMI BEACH, FLA., AND R. L. PEARSE, M.D., DURHAM, N. C.

(From the U. S. Naval Hospital, Key West, Fla., and the Department of Obstetrics and Gynecology, Southwestern Medical College)

CIRCUMSTANCES associated with potential transfer of husbands in the armed forces during World War II motivated many married couples to begin a family.[1] When pregnancy failed to occur within a few weeks or months they often assumed themselves sterile, or that their technique of union was incorrect. Women falling into this category composed nearly 5 per cent of the patients who sought obstetric and gynecologic consultation at the U. S. Naval Hospital and U. S. Naval Station, Key West, Florida, from May 15, 1942, to July 1, 1944. Many of these individuals were not informed on the physiology of reproduction. On the other hand, the consultants found little reliable information to answer the question regarding the average time required to conceive. To contribute further information to this problem is the purpose of this paper.

Clinical Material

The patients were wives of Naval, Marine Corps, or Army personnel, seen by the authors at the U. S. Naval Hospital, Key West, Florida, between Feb. 15, 1943, and June 20, 1944. Their ages ranged from 16 to 42 years. The average age was 24 years for the primigravidas and nulligravidas, and 26.7 years for the multigravidas. The figures compared favorably with Pearl's statistics[2] of 23.4 and 23.18 of the United States Birth Registration Area for 1930.

Out of nearly 1,600 women seen for obstetric or gynecologic consultation, 1,192 were selected for study. Those excluded either had some physiologic or pathologic condition precluding pregnancy; became pregnant out of wedlock; became pregnant while using contraceptive measures; were using contraception satisfactorily; or data for them was totally inadequate. Of those to be studied, 799 were pregnant and 393 were not. None used contraception. For purposes of analyses, the 1,192 were divided into three categories: Group I was composed of 318 obstetric patients selected at random. Pertinent data were available for all these. The remaining 481 pregnant women formed Group II. For these, coital rates were unknown, and 20 to 25 per cent had been separated from their husbands for periods of one to twenty-four months. Information for the 393 nongravid who constitute Group III was comparable to Group II. Among Group I were 261 primigravida and 57 multigravida. Corresponding figures for Group II were 354 and 127. The nonpregnant were made up of 251 nulligravida and 142 gravida i or more.

From each woman the date of marriage; past, marital, and family histories; rank or rate and age of the husband were obtained. All had a pelvic examination and nearly all had a complete physical and laboratory study including urinalysis, red blood count, and blood serology. In addition, one physician

(A. W. D.) questioned those in Group I individually at some time during pregnancy to determine coital rates. The frequency of sexual intercourse during the month prior to conception was accepted.

Permanent addresses given covered the 48 states. All but two women were white. Approximately 25 per cent were wives of officers, while the remainder were spouses of enlisted men. All dependents lived on an island five by one to two miles in size. Geographic description of the area has been given elsewhere.[3]

The husbands ranged in age from 18 to 49 years, with the average of 27.5 years. On the average, they were away from home one night out of three. It should be recognized that these men were picked because of their physical fitness for the Armed Forces. Therefore, they are a select group as compared to the population at large.

Results

Among Group I, 190 of the primigravidas conceived within six months, 226 in twelve months, and 249 in twenty-four months. Corresponding figures for 57 multigravidas were: 22, 37, and 49. See Table I.

Fifty-nine of the newly married women became pregnant immediately after marriage and before having another menstrual period. The fruitful intercourse in all these women, except one, occurred before the end of the third quarter of the menstrual cycle. The time of marriage with reference to the first day of the last menstural period was: 39 seven to ten days afterwards; 13 in two weeks; 6 in three weeks but 7 to 10 days before the next expected menses; and 1 five days before the next expected menses.

From Group II, 160 of the primigravidas were pregnant in six months; 257 in twelve months, and 312 in twenty-four months. In order, the figures for the multigravidas were 16, 49, and 89. Interestingly enough, a large proportion of the pregnancies that began after eleven months did so at twelve, twenty-four, thirty-six, forty-eight, and seventy-two months (79 out of a possible 172). Transfer of personnel in the Navy was made generally at 6-, 12-, 18-, or 24-month intervals. The figures suggest pregnancies might have followed shortly after reunion of husband and wife. The same observation was made among 108 pregnant women not included in the study. These individuals were using contraceptive measures up to a short time before conception occurred. On the other hand, forewarned of a separation, these couples may have decided to produce a pregnancy.

TABLE I. LENGTH OF TIME REQUIRED FOR CONCEPTION TO OCCUR AMONG 799 MARRIED WOMEN

GROUP	PATIENTS NUMBER	6 MONTHS PATIENTS		12 MONTHS		24 MONTHS PATIENTS		NO. NOT PREGNANT IN 24 MONTHS
		NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	
Primigravidas								
I	261	190	72.7	226	86.6	249	95.4	12
II	354	160	45.2	257	72.6	312	88.6	42
Multigravidas								
I	57	22	38.5	37	64.9	49	86.0	8
II	127	16	12.5	49	38.5	89	70.1	38

One hundred and thirty-eight (54.9 per cent) of the nonpregnant nulligravida were not pregnant by the end of eleven months, while the other 113 (45.1 per cent) had not conceived after twelve to seventy-two months or longer. Corresponding figures for the previously gravid patients were 39 (27.4 per cent) and 103 (72.6 per cent).

Coital rates (Table II) were comparable to those reported by Davis.[4] The impression was gained that an average of two or three coitions per week were attained in six to twelve months after marriage. There was no obvious relation between frequency of union or age of patients and time required to conceive.

Comment

In most instances, previous communications on the subject of fertility rates have been based on analysis of hospital records where emphasis usually had been directed to problems other than the time required for conception. Also, many of the case studies were gathered by numerous individuals so that questioning was haphazard. The patient was often required to depend on memory to recall facts five to ten or twenty years past. The unreliability of the human testimony vitiates the results.[5] Some of the observations recorded in this survey may be subject to the same criticism. However, an attempt was made to minimize

TABLE II. AVERAGE NUMBER OF COITIONS PER WEEK AMONG 318 PREGNANT WOMEN IN THE MONTH PRIOR TO CONCEPTION

FREQUENCY OF COITUS PER WEEK	PRIMIGRAVIDAS* 261 SUBJECTS	MULTIGRAVIDAS† 57 SUBJECTS	DAVIS'4 971 SUBJECTS
1 to 2	105	45	391
2 to 3	124	11	305
Four or more; less than 7	20		
Less than once	1	1	125
Exact data not given			60
Daily or often	11		90

*Four patients were above the age of 30 years.
†Nine were above 30 years.

inaccuracies by basing the questions on recent events and limiting the number of examiners to three. The ideal plan would be to have each newly married woman keep detailed records over long periods of time.

Many variables influence fertility: libido, coital rates, frequency of occurrence of pregnancy in relation to the physiologic possibility, contraceptive measures employed, if any, reproductive wastage, and availability and viability of ova and sperm in the female genital tract.

Libido is indirectly estimated by the frequency of sexual intercourse. The frequency of sexual contact may vary considerably with the age of the couple, with the duration of marriage, the amount of other physical activity endured, and the desire to have offspring. Although husbands were not home every night, it is believed that the temporary absences added to rather than detracted from sexual ardor. At least it is questionable whether sexual relations would have been significantly more frequent with the couple living at home continuously. The factor of climate may have played a part in Key West. Those going to torrid from more temperate zones have a temporarily accentuated sexual activity.[6] Outdoor workers are supposed to be more active sexually than those occupied indoors, and laborers more than professional people.[2] The clientele of this study received maximal amounts of fresh air, but were usually not as physically active as a day laborer.

Although coitus was more frequent in early marriage, it is noteworthy that the average patient did not become pregnant for a matter of months. The same idea has been confirmed by Stix and Notestein.[7] Our figures approximate more nearly those recently reported by Russell[8] than those given by Pearl. The former found among 197 first conceptions and 96 second conceptions nearly two-thirds of the pregnancies started within three months following natural coitus, while the latter's corresponding percentage was over one year. The mean number of months before pregnancy began plotted against the various frequencies of coitus gave a similar product. Stix and Notestein give a partial explanation on the basis that complete entry may not be accomplished the first few weeks. Williams[9] and Moench,[10] in addition, have shown that excessive sexual activity on the part of the male may detract rather than enhance conception. It is probable that an ovum does not live more than twenty-four hours, and sperm are capable of fertilizing only twenty-four to seventy-two hours.[11] Theoretically, a normal woman can become pregnant only one to three days each month.[12] Generally, women are physiologically sterile for an average period of three months after delivery because ovulation does not occur.[13, 14] Therefore, the apparent sterility of a parous individual as compared to a primigravida is relative. Coitus at the average rate of 2 to 3 times per week would many times fail to coincide with ovulation. In other words, the important thing is when sexual union occurs, not how often.

Summary

From a survey during 1943 and 1944, of 318 pregnant (261 primigravidas and 57 multigravidas) married, white women ranging in age from 16 to 42 years, and living in a semitropical climate with husbands who were members of the Armed Forces, and away from home one night out of three, it was found that 86 per cent of the primigravidas conceived in the first year of married life. The corresponding figure for 57 multigravidas was 64.9 per cent. Contraception was not employed by these couples. Sexual union was experienced more or less by chance with relation to the time of ovulation, but on an average of two to three times a week.

Although all data were not available for 481 other pregnant and 393 nonpregnant women, using no contraception, results collected therefrom, correlated with those above, substantiate the conclusion that the majority of fertile couples can expect pregnancy to begin within twelve months after marriage. Multigravidas will require a slightly longer time to conceive than primigravidas because there is a period of relative sterility following the previous pregnancy.

References

1. Preview of the Postwar Generation, Fortune 27: 116, 1943.
2. Pearl, R.: The Natural History of Population, Oxford University Press, N. Y., 1939.
3. Diddle, A. W.: The Effect of Travel on the Incidence of Abortion, Am. J. Obst. & Gynec. 48: 354, 1944.
4. Davis, K. B.: Factors in the Sex Life of Twenty-two Hundred Women, Harpers, New York, pp. 430, 1929.

5. Hartman, C. G.: Personal communication.
6. McCartney, J. L.: White Men in the Tropics, Diseases of the Nervous System **5:** 133, 1944.
7. Stix, R. K., and Notestein, F. W.: Controlled Fertility, Williams and Wilkins, Baltimore, 1940.
8. Russell, C. S.: Human Sterility, Lancet **1:** 300-303, 1946.
9. Williams, W. L.: Abortion in Animals. Chapter III, Abortion, edited by F. J. Taussig. C. V. Mosby Co., St. Louis, 1936.
10. Moench, G. L.: The Longevity of the Human Sperm. AM. J. OBST. & GYNEC. **38:** 163, 1939.
11. Hotchkiss, R. S.: Fertility in Men. J. B. Lippincott Co., Philadelphia pp. 143, 1944.
12. Barton, M., and Weisner, B. P.: Waking Temperature in Relation to Female Fecundity. The Lancet **249:** 663, 1945.
13. Davis, M. E.: The Clinical Use of Oral Basal Temperature; J. A. M. A. **130:** 929, 1946.
14. Booth, Marguerite: The Time of Reappearance and the Character of the Menstrual Cycle Following Gestation. Thesis. Yale University, 1935.

THE ROLE OF NUTRITION IN PELVIC VARIATION*

HERBERT THOMS, M.D., NEW HAVEN, CONN.
(From the Department of Obstetrics and Gynecology, Yale University School of Medicine)

VARIATIONS in the shape of the adult female pelvis have a major interest to obstetricians because roentgen studies have shown that even in healthy adults there exists wide differences in pelvic architecture. Furthermore, some of these so-called "normal variations" may have a decided influence on labor and their delineation before that event often reveals highly useful information. The present communication is concerned chiefly with an inquiry into the reason why these variations occur and why the childhood type of pelvis, i.e., dolichopellism, is preserved in enlarged form in some adults but not in others. It presents evidence that, among other factors, nutrition, especially during the puberal period of growth, apparently plays a major etiologic role.

Approach to the subject is best served by considering certain facts concerning the shape of the pelvis in infancy and childhood. The shape of the pelvic inlet in early childhood in both sexes is characteristically elongated anteroposteriorly, or *dolichopellic* (Fig. 1), and if a pelvis of this type were to grow symmetrically it would have a similar shape in adult life. From this it would appear that the round or flattened forms of the adult pelvic inlet may arise as a result of either of two mechanisms; an excessive growth laterally, that is, of the transverse diameter, or a diminished growth anteroposteriorly. From studies of the author and associates, it seems apparent that the lessening or incomplete development of the anteroposterior diameter is the more important mechanism, increasingly so as the degree of flattening becomes more extreme.

For purposes of classification we may say that the tendency of a pelvis to retain most of the relationships of fetal and childhood conformation and thus remain relatively elongated anteroposteriorly may be spoken of as dolichopellism (dolicho = long), while the tendency in a pelvis to become broadened transversely and short anteroposteriorly is that toward platypellism (platy = broad or flat). A simple and useful classification of pelves, therefore, can be based upon these anteroposterior and transverse pelvic relationships, as suggested by Turner in 1885.[1] The relative size of these two dimensions is most conveniently expressed as the pelvic index. This index is the anteroposterior diameter of the pelvic inlet times 100 divided by its maximum transverse diameter. By means of this index it is possible to group together pelves which show the same degree of anteroposterior flattening or elongation regardless of their absolute size. Turner classified pelves into three types on the basis of

*This study was made possible through grants from the Clinical Research and Teaching Funds of Yale University School of Medicine.

their pelvic index. Those with an index of 95 or more he called dolichopellic, those with an index from 90 to 94.9 mesatipellic, and those with an index less than 90 he termed platypellic. For anthropologic purposes the use of the pelvic index is ideal and would be useful in clinical evaluation, except that it is a little unwieldy because it cannot always be estimated by simply viewing dimensions.

A simpler and more useful plan for classifying pelves based upon the principle of the "pelvic index" follows. In this method pelves are divided into four general groups:

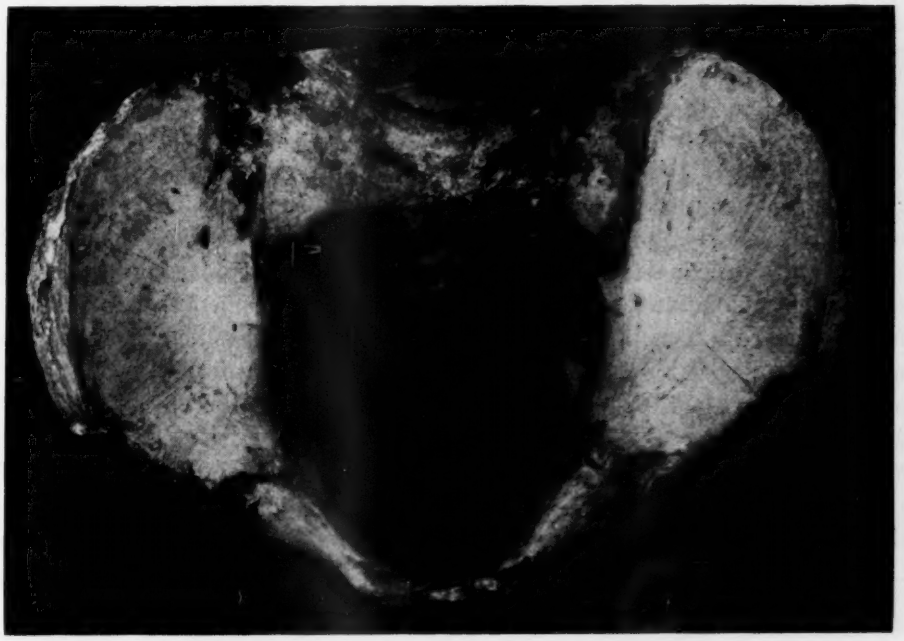


Fig. 1.—Dolichopellism in pelvis of child of 3 years (female). Anteroposterior of inlet, 6.1 cm.; transverse of inlet, 5.5 cm.

1. *Dolichopellic type:* The anteroposterior diameter of the inlet is longer than the transverse.

2. *Mesatipellic type:* The anteroposterior and transverse diameters of the inlet are equal or the transverse diameter is no more than 1 cm. longer than the anteroposterior.

3. *Brachypellic type:* The transverse diameter is more than one and less than 3 cm. longer than the anteroposterior diameter.

4. *Platypellic type:* The transverse diameter is 3 cm. or more longer than the anteroposterior diameter (Fig. 2).

We have found this method of pelvic classification clinically useful as a ready means of identifying pelves for purposes of description and record. For purposes of completeness, certain morphologic characteristics, not associated with mensuration, may be added to the pelvic survey, such as the wideness or narrowness of the pelvic forepart, sacrosciatic notch, etc.

From our investigations of adult pelves in both sexes, it appears that at the present time methods of classification based on sex characters may be confusing and in some instances not altogether sound. This is in view of the fact that our studies in male pelves show essentially the same variations that we find in the female.

Thus, in the investigations of Gruelich and the author[2] we state, "Our findings indicate that the pelvic inlet of the male is as variable in shape as that of the female. . . . It is evident, therefore, that there is in our population at least no one type of male pelvis, just as there is no one type of female pelvis." And again, "It is evident from the tracings that the shape of the pelvic inlet of most of the men of our series is quite different from that described in the textbooks as typically masculine. Indeed, the pelvic inlet of some of our males so closely resembles that of some of the student nurses of our earlier series that it would be difficult in certain cases to determine the sex of the individual from the shape of the pelvic inlet alone."

It seems clear that, while certain sex characteristics of male and female pelves can be accepted as more or less constant, others formerly thought to be constant are highly questionable. Added to this is the fact that "normal" variations in anteroposterior and transverse relationships are apparently present in both sexes in wide distribution. That the anteroposterior and transverse relationships can form a suitable basis for clinical classification has been recently re-emphasized by Nicholson,[3] who states: "Obstetricians have of late devoted a great deal, probably too much attention to the classification of the pelvis by its shape. Accepting the fact that the lengths of the pelvic diameters, in common with other anatomic measurements, are normally distributed, we may from the given figures calculate the corresponding figures for the pelvic index which after all is the chief guide to the shape of the pelvis."

TABLE I. INCIDENCE IN 107 YOUNG GIRLS

AGE	NUMBER OF CASES	DOLICHOPELLIC (%)	MESATIPELLIC (%)	BRACHYPELLIC (%)
5	2	100.0		
7	1	100.0		
9	4	75.0	25.0	
10	25	72.0	28.0	
11	21	86.0	14.0	
12	18	50.0	33.3	16.7
13	14	35.5	50.0	14.5
14	18	27.8	55.5	16.7
15	4	25.0	75.0	

TABLE II. INCIDENCE OF PELVIC TYPES

	100 NURSES (%)	WHITE 1,100 "CLINIC" WOMEN (%)	100 NEGRO WOMEN (%)	WHITE 107 CHILDREN (%)
Dolichopellic	37.0	18.6	29.0	59.9
Mesatipellic	46.0	49.9	43.0	33.6
Brachypellic	17.0	32.2	25.0	8.3
Platypellic	--	3.2	3.0	--

Some idea of the distribution of these types in several groups of our population may be gathered from the statistical information gathered through roentgenologic studies by the author and associates[4-6] shown in Tables I and II.

Our knowledge of the influence of endocrine forces on pelvic architecture may be aided by certain observations found in a report on Mental and Physical Growth in Pubertas Praecox published in 1939 by Gesell, Thoms, Hartman,

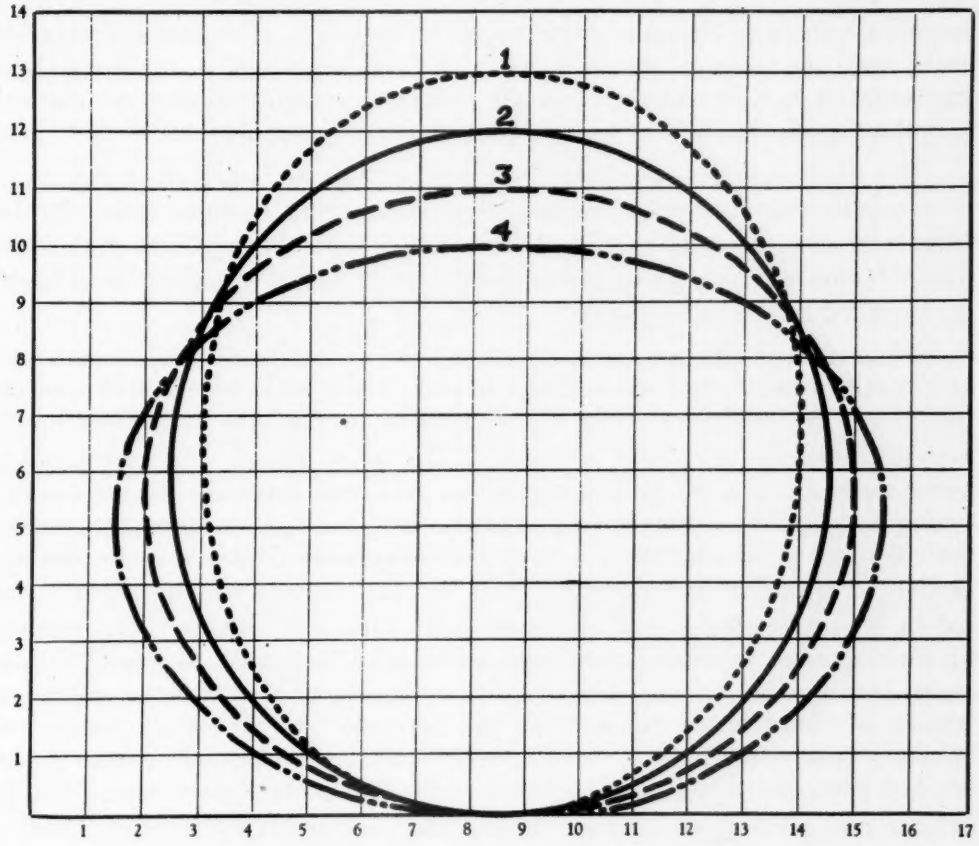


Fig. 2.—Diagram showing usual pelvic variations in four groups. (See text.)

and Thompson.[7] This report was based primarily upon fifteen years of observation of a patient with a well-defined, uncomplicated pubertas praecox who showed signs of pubescence in the first year of life and menstruated at the age of 3 years and 7 months. She died at the age of 18 years and 7 months of an infection following the removal of a cerebellar fibrillar astrocytoma. Growth in height practically ceased at the age of 11 years. At the age of 18 the pelvis was of a typical dolichopellic type and posteriorly exceptionally spacious. Dolichopellism was not extreme, the pelvic inlet being well rounded in both forepart and hindpart, the measurements being anteroposterior diameter 12.00 cm., transverse diameter –11.25 cm. If the oval or brachypellic type pelvis results chiefly from sex hormone influence, it would be fair to assume that in this case a marked tendency toward platypellism should be present.

This raises the question as to whether the oval or brachypellic type pelvis may not be the result of certain deficiencies in nutrition, especially during the puberal period when nutritional requirements seem to be in more delicate balance than at other periods of growth. In a recent statement, Johnson[8] stated, "The margin of safety to insure storage (of calcium) in girls at puberty is small . . ." and, "The comparative rarity of clinically recognizable rickets beyond infancy may account for the casual attitude of the average pediatrician toward adequate provision of calcium and vitamin D." The question suggests itself, may not these relatively flattened pelves (brachypellic, platypellic) be the result of calcium imbalance, slight rickets if you will, during the puberal period when the demands of skeletal growth are so increased?

The rachitic pelvis, resulting from severe types of rickets, is well known. It is manifested chiefly by marked platypellism, and in some cases the deformity is so great as to greatly shorten and almost obliterate the anteroposterior diameter. Anteroposteriorly such a pelvis seems collapsed upon itself, the so-called osteomalacic pelvis.

Flattening of the pelvis, either to a mild or severe degree, could occur as a result of one or two mechanisms or both, namely, as the result of mechanical force, i.e., weight bearing, or differences in the rate of growth under rachitic influence of certain portions of the pelvic bones. An investigation along these latter lines by the author[9] in 1936 was entitled, "Is the oval or female type pelvis a rachitic manifestation?" This paper, therefore, raised the question as to whether the oval or brachypellic type pelvis, so long regarded in anatomic and obstetric texts as the "normal female pelvis," was not in reality abnormal, and the mesatipellic and dolichopellic types, because of their greater combined incidence, essentially "normal" types. Furthermore, because the writers of such texts apparently were unaware of the existence of these latter types, "the predominant type of pelvis which was formerly seen in clinics may have actually changed in character within a generation. When alterations are considered in environment surrounding female infants and adolescent children during the past twenty-five years, changes brought about not only by a great difference in diet, but by such influences as outdoor exercise and life in the open, it must be admitted that the environment for this group has changed indeed during that period. When one further considers the sedentary habits, the type of clothing, the diet, and general restrictions that previously were a part of the life of female infants and children, may one not speculate as to the effect of such an environment on the adult form of the female pelvis? That changes in environment can effect skeletal changes in a large proportion of a population is witnessed in recent years by the extraordinary lessening of the incidence in children of severe rachitis." Further evidence which would suggest such changes is found in the statement of Hooton,[10] who says, "Nearly everyone knows that Americans are getting taller, generation by generation," and the studies compiled by Riggs[11] showing the significant increase found in the statures of entering freshmen in the northeast, midwest, and northwest.

The author's communication on the oval pelvis was based on a study of the pubic and iliac portions of the *line of terminal length* in the pelves of fifty women. The terminal length theory of Breus and Kolisko[12] may be briefly stated.

These authors maintain that the relative flattening of the superior strait in the adult pelvis is due not so much to mechanical forces, but to differences in rate of growth before puberty of certain portions of the pelvic bones. They pronounce particular importance upon the so-called terminal length of the innominate bone. They point out that if we saw through the innominate bone at the level of the iliopectineal line and view the sawn surface of the upper half, we shall see that the surface may be arbitrarily divided into three parts, the sacral. iliac, and pubic portions. These are practically of equal length, the whole being in the neighborhood of 20 cm. In the period of development these portions arise from the following: the sacral portion from the cartilage of the iliac crest, the iliac portion from the Y-shaped cartilage of the acetabulum, and the pubic portion from the same cartilage and from that of the symphysis. These authors contend that the variations in the rate of growth of these three portions are the most important factors in determining the shape of the pelvis and that mechanical factors play a distinctly minor role.

They further state that in rachitis the pubic portion retains its normal proportions, the iliac portion being greatly shortened, and the sacral portion slightly shortened. When this change is present, they state that it is almost pathognomonic of rachitis." This roentgenologic study of 25 oval (brachypellic) and 25 mesatipellic and dolichopellic pelves showed that in nearly all instances the iliac portions in the former were from 1.00 cm. to 2.25 cm. shorter than the pubic portions. The paper concluded thus, "From available information concerning pelves in aboriginal people living in climates in which rachitis does not occur, it appears evident that the round type pelvis is greatly predominant. Furthermore, it seems apparent that the unusual incidence of the round and the anthropoid types in the women of our population must be explained on grounds other than those based on such influences as race and constitution. The above study would appear to be important evidence toward a definite answer to this problem."

In a paper entitled, "What Is a Normal Pelvis," published in 1934, the author[13] presented the views of other observers which are appropriate to the present discussion and are here restated.

"Stoney and Vaughan have suggested that oval pelves are not truly the result of racial influence but are caused by the conditions of life in modern civilization. The former says that the oval pelvis of the civilized woman is due to lack of light and vitamin D. Vaughan emphasizes the causal relationship of other factors such as posture (especially in children) and points out that differences in pelvic development may be noted in the same race living under different conditions. Thus, women of India and China who work outdoors have easy labors, while those living in cities or in seclusion have difficult labors. Jarcho quotes the Carnegie Trust Report for 1917, which emphasizes the 'easy labors and large families among the Highland women who, barefooted, haul in the nets with the men, follow the plough and engage in field work.' Incidentally, I may add that their diet probably consists largely of fish, which is a well known source of vitamin D.

"The effect of civilization on an aboriginal people living under poor hygienic conditions in large cities is nowhere better shown than in the studies of J. Whitridge Williams, who emphasizes the effect of such an environment

in producing 'rachitis and imperfect general development which play so conspicuous a part in the genesis of abnormal pelves in the colored race.'

"Miller, in speaking of Williams' studies of rachitic pelves in the Negro women of Baltimore, makes the comment that he (J. W. Williams) works in a city which is essentially Northern in mode of life and his patients live in tenements and in typical tenement surroundings, whereas the Negro of the far South, both in the city and the surrounding country, whatever else he may lack has an abundance of fresh air and sunshine, the two arch enemies of rachitis. Levey's report from the Touro Clinic I might add, corroborates these findings as to the relatively small percentage of contracted pelves among colored women in this part of the country."

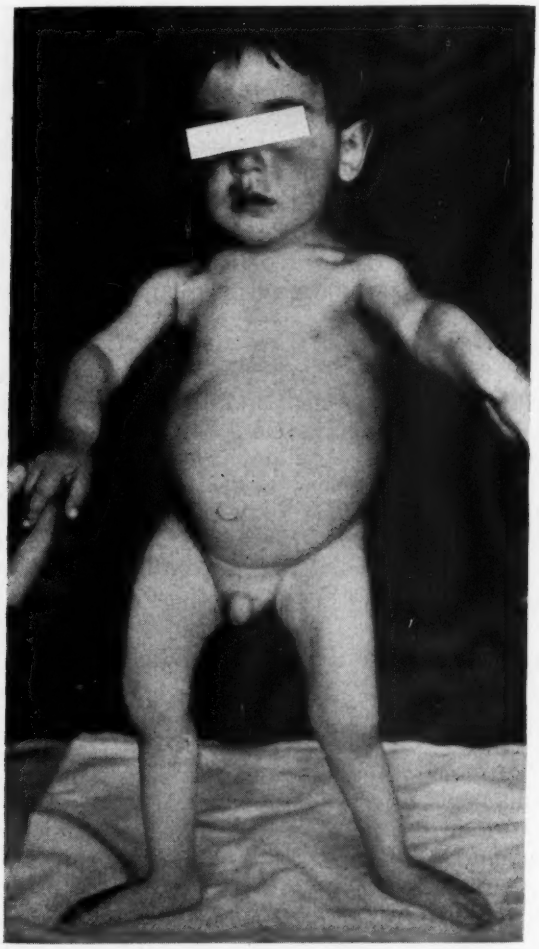


Fig. 3.—Child at 3 years, 3 months showing classic signs of rickets.

A recent study by Dunham and the author[14] on "Effects of Severe Rickets in Early Childhood on Skeletal Development in Adolescence" shows that early childhood rickets may or may not leave evidence in the matured pelvis. Our summation of findings was,

For ten children in whom a condition diagnosed as severe rickets had been present in early childhood pelvic roentgenograms were made during

adolescence. On the basis of the pelvic diagnosis, these ten children fall into two groups: five children who had rachitic pelves in adolescence and five who had nonrachitic pelves.

What evidence is there of a relationship between the early histories of these two groups of children and their status in adolescence?

In regard to the age when rickets was known to be active, it was found that of the five adolescent children who had rachitic pelves three were more than 4 years of age when active rickets was diagnosed; of the five whose pelves were normal four were less than 3 years of age when active rickets was diagnosed. *Apparently, the older the child at the time when active rickets of a moderate or severe degree is present, the greater is the chance that the pelvis will show rachitic deformities in adolescence.*

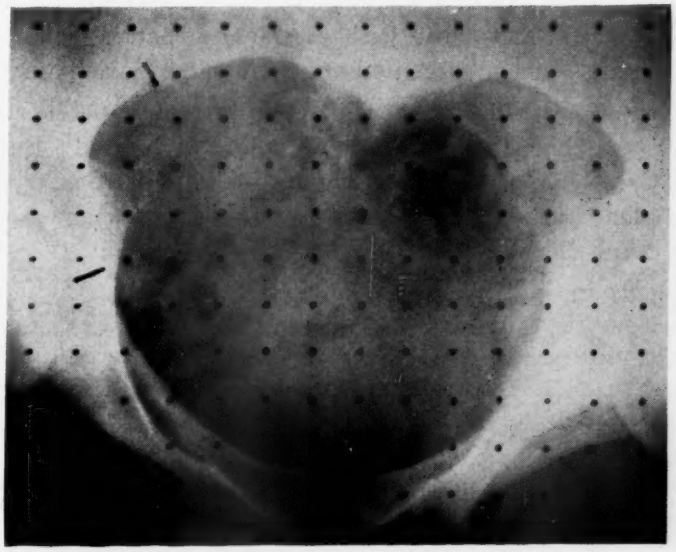


Fig. 4.—Pelvic inlet roentgenogram of child shown in Fig. 4 taken at age 19 years. Typical rachitic pelvis: anteroposterior 7.8 cm., transverse 11.5 cm. (Note shortening of iliac portion—line of terminal length.)

In regard to physical development in early childhood, as indicated by the age at which the children were able to sit and to stand, no striking differences were found in the two groups. All the children were able to sit alone before they reached 1 year of age, and three children in the group with rachitic pelves and two in the group with nonrachitic pelves did not walk until they were 2 years of age or older.

Physical examinations showed that all ten children had in adolescence some deformity of the lower extremities. In the children who had had severe rickets in early childhood knock-knees were associated more often with rachitic deformities of the pelvis than were bowlegs.

Severe or moderate deformities of the spine or of the lower extremities were found in early childhood as often in the group with normal pelves in adolescence as in the group with rachitic pelves. Differences in the two groups

were found, however, in the incidence of knock-knees in early childhood: of the five children with rachitic pelves in adolescence two had had knock-knees in early childhood and two had had bowlegs (the status of one was not known). Of the five children with normal pelves, none had had knock-knees in early childhood. These observations suggest that if knock-knees were present in early childhood the pelvis in adolescence is more likely to show the deformities of rickets than if bowlegs were present in early childhood. It is perhaps significant that one of the children who had had bowlegs in early childhood had in adolescence an unusual deformity that resulted in outward curvature of one leg and inward curvature of the other.

As is well known, high ratios of sitting height to standing height are considered evidence of retardation of growth of the lower extremities. High ratios were found for all but one of the children; this observation includes both the children with rachitic and those with nonrachitic pelves. One child with a rachitic pelvis had a normal ratio, and one was not measured.

Further evidence of the influence of environment in pelvic change is seen in "A Study of Pelvic Type and Its Relationship to Body Build in White Women," by Greulich, Twaddle, and Thoms,[5] in which a comparison was made among 104 student nurses, a much more privileged economic group than that of 582 primigravid white women of clinic status.

The incidence in these groups is shown in Table III.

TABLE III

	104 STUDENT NURSES	582 CLINIC WOMEN
Dolichopellic	37.5%	15.0%
Mesatipellic	44.2%	44.8%
Brachypellic	18.2%	34.3%
Platypellic	-----	5.6%

A further comparison "of body build and pelvic type in 132 of the clinic women and the 104 student nurses disclosed the following relationships: (a) The women with long oval pelves were predominantly tall, long headed, and broad shouldered; the width of the pelvis between the iliac crests, and of their hips between the trochanters were smaller in proportion to the width of their shoulders than in women of the other pelvic types; they had the largest average external conjugate diameter. (b) The women with transversely elongated pelves were, on the average, the shortest of the series and they had the broadest heads, the narrowest shoulders, the widest pelves and hips in proportion to the width of their shoulders, and the smallest external conjugate diameter. (c) The women with round pelves were approximately intermediate between the other two groups in all these dimensions. There was, however, so much variation in these external dimensions between student nurses and clinic women of the same pelvic type that, in our opinion, it would be quite hazardous to attempt to predict pelvic type on the basis of those dimensions in individual cases in a population as heterogeneous as that of this country.

The high incidence of long oval and of round pelves among the largest women of both groups suggests the possibility that nutritive and other factors

which make for the attainment of maximum normal growth tend to prevent that degree of anteroposterior flattening of the pelvis which has come to be regarded as characteristically feminine.

Evidence of the role which nutrition probably plays in pelvic architecture is seen in a recent report by Allen[15] in a study of 244 New Zealand women, who states that the series is representative of New Zealand-born women of childbearing age in his district, and that there is no reason to suppose that it is not fairly representative of New Zealand-born women as a whole.

In his group he found the following incidence, separated according to Turner's original classification, as follows:

Dolichopellic—(index over 95)	54.2%
Mesatipellic—(index 90 to 95)	18.2%
Platypellic—(index below 90)	27.6%

His opinion regarding etiology coincides quite closely with the author's, and is here quoted:

"It is interesting to speculate upon the reasons underlying this variation, which is dependent primarily upon the finding that the local pelvis has a relatively and absolutely long obstetrical conjugate diameter. It seems possible that there is more truth in Thoms' suggestion that adequate nutrition can influence pelvic shape than is generally thought. It has been established that until the age of puberty there is very little difference between the shape of the pelvis in the two sexes, but that at puberty the pelvis very rapidly takes on sexual characteristics. It is conceivable that during this period of rapid growth nutritional disturbances might exercise a very profound effect. If these disturbances were to lead to any softening of the bones, the diameter which would predominantly be affected would be the conjugate, because of its relation to the axis of weight-bearing.

"It also appears possible that the responsible factor may be a subclinical deficiency of vitamin D. I discover that this suggestion has already been made by Thoms who regards the oval or female type pelvis as definitely a rachitic manifestation. He quotes the theory of Breus and Kolisko who consider that in rickets there is a pathognomonic relative shortening of the iliac component of the circumference of the pelvic brim. Thoms himself has shown that such a shortened iliac portion is present in the female type of pelvis, and further points out that in aboriginal people living in climates where rickets does not occur, the round type of pelvis predominates. Although, therefore, the statement is commonly made that the round pelvis is normal in Negroes and Hottentots and it is implied that this is a racial feature, it is possible that it is due to an anti-rachitic environment.

"The findings here reported lend some support to this theory. The local female almost never in her life suffers from malnutrition of any sort unless for some deliberate reason. The population is rural and semi-rural in type, and dairying is the only major industry. The average per capita consumption of butter for New Zealand as a whole for the last three years (1939-42) is given as 42 pounds per annum, and no doubt it is higher than this locally. The hours of bright sunshine in New Plymouth over the past 31 years have averaged 2,247 per annum. The local female is, therefore, highly unlikely to suffer from any vitamin D deficiency: and, indeed, only two cases of rickets,

both in the same family, have been seen in this district during the last three years. Racial variations can scarcely explain the difference between the New Zealand and English figures, because the local stock is predominantly British, and it is scarcely reasonable to assume that the mere accident of birth in New Zealand could produce such an atavistic reversion in the absence of some environmental factor. I believe, therefore, that the shape of the pelvis is determined more by environment and diet than by inherited racial tendencies."

Another recent study bearing out essentially the same conclusions is that of Nicholson[3] who, in a roentgenologic study of the anteroposterior diameter of 640 women in England, makes this statement: "The length of the conjugate diameter is very considerably influenced by nutrition, and, in the absence of any large population which up to now can be considered as fully nourished in childhood, it is still quite impossible to determine the mean to which the measurement tends." Nicholson also states, "Pelvimetry by radiology in 640 cases is analysed to show that the length of the conjugate diameter of the female pelvis is very sensitive to nutrition, and the figure quoted in textbooks of anatomy for this diameter is too low."

In recapitulation these statements are offered:

1. Roentgenography has revealed that the adult female pelvis is subject to considerable variation in its anteroposterior relationships. These variations have a definite clinical interest to the obstetrician, for, in instances they may have a pronounced effect upon the course of labor.

2. The so-called "normal" female pelvis of anatomical texts needs revision because the architecture usually described is that of the brachypellic or oval type, which is present in about only one-third of adult women according to evidence presented here.

3. The pelvis of infancy and childhood in both sexes is essentially similar as far as anteroposterior relationships are concerned; until a time just preceding the puberal period they tend to grow symmetrically. At that time changes in anteroposterior and transverse relationships take place which have been described. These changes are apparently the result of two major influences, sex hormonal and nutritional. It would seem on first appraisal that such hormonal influence was the dominant factor because of the well-known somatic and psychic phenomena associated with the puberal period. Nevertheless, wide variations in pelvic architecture are present in our adult population which are apparently unrelated to such phenomena.

4. Evidence is given to show that nutritional influences during the puberal period seem also to have a major role in these changes in anteroposterior and transverse pelvic relationships, as shown by the studies here presented. This role seems to be associated closely with calcium and vitamin D requirements.

5. The evidence presented here emphasizes the need for further study of the nutritional requirements of the growing child, particularly during the puberal period. It also emphasizes the importance of using that knowledge of this subject which we already have to the end that the nutrition needs of the growing child be met in a manner suitable to the requirements of normal growth.

References

1. Turner, William: J. Anat. & Physiol. 20: 125, 1886.
2. Greulich, W. W., and Thoms, H.: Anat. Rec. 73: 289, 1939.
3. Nicholson, C.: J. Anat. 79: 131, 1945.
4. Greulich, W. W., and Thoms, H.: Anat. Rec. 72: 45, 1938.
5. Greulich, W. W., Thoms, H., and Twaddle, R. C.: J. A. M. A. 112: 425, 1939.
6. Thoms, H.: Am. J. Obst. & Gynec. 52: 248, 1946.
7. Gesell, A., Thoms, H., Hartman, F. B., and Thompson, H.: Arch. Neurol. & Psychiat. 41: 755, 1939.
8. Johnston, J. A.: Am. J. Dis. Child. 67: 265, 1944.
9. Thoms, H.: Am. J. Obst. & Gynec. 31: 111, 1936.
10. Hooton, E. A.: From Riggs, vide infra.
11. Riggs, F. B.: Tall Men Have Their Problems Too, Cambridge, 1943, privately published.
12. Breus, C., and Kolisko, A.: Die Pathologischen Becken formen, Leipzig u. Wien, 1904.
13. Thoms, H.: J. A. M. A. 102: 2075, 1934.
14. Dunham, E. C., and Thoms, H.: Am. J. Dis. Child. 69: 339, 1945.
15. Allen, E. P.: New Zealand M. J. 43: 116, 1944.

ANESTHESIA IN OBSTETRICS*

J. P. GREENHILL, M. D., CHICAGO, ILL.

IT IS safe to say that analgesia and anesthesia in obstetrics are used much more extensively in the United States than anywhere else in the world. This is fortunate for American women, but the blessing is far from a perfect one. Every year a significant number of babies and many mothers die as the direct or indirect result. In most instances the deaths result from injudicious use, either because the choice of the agent was erroneous, or because too much was used. However, occasionally even when a satisfactory dose of the proper analgesic or anesthetic agent was used a fatality resulted.

By the term analgesia I mean relief of pain, and by the word anesthesia I imply loss of sensation or feeling. There may be general loss of sensation such as that produced by inhalation or intravenous anesthesia or local loss of feeling such as that induced by spinal, caudal, or direct infiltration anesthesia. If loss of consciousness is used as the criterion of anesthesia, then the only anesthetic agents are those administered by the inhalation and intravenous routes. All the pain relievers, including spinal, caudal, and local, would then be called analgesics and not anesthetics. Of course, inhalation agents are both analgesic and anesthetic.

I shall limit my remarks to analgesia and anesthesia used during the second stage of labor and operative deliveries.

The incidence of deaths which occur under practically all types of anesthesia is not generally known. In 44,894 anesthesias given at the Wisconsin General Hospital by well-trained anesthetists, Waters and Gillespie reported 47 deaths, an incidence of 0.1 per cent or one death for about every thousand cases. Gillespie reported 227,546 collected cases of anesthesia with a death rate of 0.12 per cent, practically the same as that among the Wisconsin series.

The anesthetics which are used for parturient women are of five types: (1) inhalation, (2) intravenous, (3) caudal, (4) spinal and (5) local, infiltration anesthesia.

I. Inhalation Anesthesia

The inhalation anesthetics which are generally employed are the volatile agents, chiefly ether but sometimes chloroform, and the gaseous anesthetics, especially nitrous oxide and also ethylene and cyclopropane.

1. *Ethyl ether* is the most widely used anesthetic in obstetrics in the United States. The reason for this is most likely the low cost of ether, its low mortality, ease of administration, and wider margin of safety than with most of the other anesthetic drugs. When ether is used for analgesia its effect is primarily psychic, because if enough ether is used to produce adequate analgesia the intensity of the uterine contractions will diminish. The disadvantages of ethyl ether are: induction is slow and excitement is apt to occur; there is slight damage to the liver, especially if associated with anoxemia; the drug irritates

*Read before the New York Academy of Medicine, Section of Obstetrics and Gynecology, Nov. 26, 1946.

the respiratory tract and is contraindicated in patients with infection of the upper part of the respiratory tract, pulmonary disease, acidosis, diabetes, or increased intracranial pressure; ethyl ether is inflammable, and heightened depth of anesthesia produces increasing uterine inertia, and considerable nausea and vomiting follow its use.

2. *Divinyl ether* or *vinethene* is a recently discovered saturated ether which vaporizes more rapidly than ethyl ether. Induction of anesthesia can be completed in one to three minutes instead of the ten to thirty minutes required for ethyl ether. Nausea and vomiting are less, and emergence to consciousness is more rapid than with ethyl ether. The disadvantages of divinyl ether are the possibility of hepatic damage, especially if attended by anoxia, and the difficulty of maintaining depth of anesthesia. Sufficient depth of anesthesia for an episiotomy and repair is quickly possible with divinyl ether, but it is not particularly successful for long operative procedures. It should not be used for more than thirty minutes.

3. *Chloroform* is portable, easy to administer, and inexpensive. However, its use is limited in the United States because of its toxic effects on the liver and heart and its weakening effect on the force of uterine contractions.

4. *Nitrous oxide* is used extensively in obstetrics both for analgesia and anesthesia. It is important to avoid anoxia and cyanosis because of the baby. When properly used as an analgesic at the end of the first stage or during the second stage uterine contractions are not weakened. In fact the relief from pain often tends to shorten labor because the uterine contractions seem to be more effective. For total anesthesia from 80 to 90 per cent of nitrous oxide and from 20 to 10 per cent of oxygen should be used. When oxygenation is adequate nitrous oxide has no effect on the child. The chief drawback of this agent is its limited scope of depth. The complications and mortality which have been associated with nitrous oxide invariably resulted from insufficient oxygen. Even a slight degree of anoxia may result in damage to the mother and/or the child. When relaxation is insufficient with nitrous oxide, ether is often added.

5. *Ethylene* is used chiefly in the Middle West. It produces more relaxation than nitrous oxide and has no adverse effects on the heart, liver, kidneys, or lungs. Its disadvantages are the same as those of nitrous oxide, in addition to explosibility and an increase in nausea and vomiting during recovery from its anesthetic effect.

6. *Cyclopropane* produces good muscular relaxation, acts rapidly, is pleasant to inhale, and may be used for both analgesia and anesthesia. Adequate anesthesia for all obstetric procedures may be obtained with it. Adverse effects from it have not been observed on the liver, kidneys, or lungs. Both induction of anesthesia and recovery are rapid. Nausea and vomiting occur with about the same frequency as with ethylene, but are less frequent than with ether. The disadvantages of cyclopropane are its explosibility, a conjectural effect on the heart, the necessity of a complicated apparatus, and a trained anesthetist. Of all the inhalation anesthetics, I prefer cyclopropane.

Effect of Inhalation Anesthetics on the Uterus.—Nitrous oxide and ethylene have little effect on uterine contractions; in fact, it sometimes appears that they strengthen them. When uterine contractions are tumultuous or too acutely painful, nitrous oxide or ethylene anesthesia will often moderate them and actually hasten delivery. All other inhalation anesthetics tend to diminish the strength of the contractions. Chloroform and ethyl ether cause uterine inertia after prolonged use. Light cyclopropane anesthesia has no effect on the uterus, but in the deeper planes it progressively decreases the force of uterine contractions.

Aspiration of Vomiting During General Anesthesia.—One of the greatest hazards of inhalation anesthesia for obstetric patients is the aspiration of vomitus with resultant aspiration pneumonitis. Spaid pointed out that complications from aspiration are most frequent in women in labor. Often the parturients go into labor after a full meal and are further given considerable food and fluids during labor. Should labor be unusually long or difficult, necessitating energy-giving foods, the optimal calories should be supplied by dextrose solutions given intravenously. In this way the patient is ready for general anesthesia. A therapeutic dose of atropine sulfate, given hypodermically when the patient is taken to the delivery room, will usually lessen salivary secretions during the anesthesia. Aspiration of vomitus is serious, as evidenced by the 33.3 per cent mortality in Hall's collected series of fifteen cases.

The incidence of dilatation of the stomach in women in labor is much higher than is usually realized. This atony predisposes to the eructation of massive amounts of vomitus as soon as the protective pharyngeal reflex is lost during general anesthesia. Extremely light "in and out" anesthesia is also conducive to vomiting. Every delivery room should be equipped with an efficient suction apparatus kept ready for instant use. Promptly placing the patient in the Trendelenburg position and suctioning have been lifesaving. Tracheobronchial aspiration by means of bronchoscopy may be necessary. When evidence of gastric dilatation exists, gastric lavage should be used before a general anesthetic is given.

II. Intravenous Anesthesia

Pentothal sodium is an extremely short-acting barbiturate which is now popular as an anesthetic agent, particularly for low forceps deliveries and for cesarean sections. In the latter operations the pentothal anesthesia is withheld until just before the uterus is incised. Local infiltration anesthesia is used up to this point. This manner of administering pentothal sodium safeguards the baby from a too high concentration of barbiturate with a consequent sluggish respiratory response. Intravenous pentothal sodium anesthesia is not satisfactory for spontaneous deliveries. In forceps deliveries and in cesarean sections, done entirely under intravenous anesthesia, the anesthetic should not be given until actual delivery is attempted because of the possible harm to the baby. Therefore, skin preparation, draping, and catheterization must all be completed before anesthesia is begun. This anesthetic may also be used for manual removal of the placenta and for sterilization operations.

III. Caudal Anesthesia (Caudal Analgesia)

Caudal and paravertebral anesthesia in obstetrics were first suggested by Cleland. Continuous caudal anesthesia or analgesia was introduced by Hingson and Edwards. The advantages of continuous caudal analgesia are the absence of general toxicity, complete absence of the sensation of pain during uterine contractions, and no deleterious effect on the baby, except that which may follow a decided drop in the blood pressure of the mother. Caudal analgesia is helpful in cases of toxemia because it produces a hypotension owing to vasomotor block with associated peripheral vascular dilatation. Deaths directly attributable to the procedure have occurred even in the hands of those experienced with the technique. Likewise, nonfatal complications have been reported; among them "near deaths" requiring prompt and energetic resuscitation, local and general infection, intravenous injection of the drug, idiosyncrasy, injury of the nerve roots, breaking of a needle, precipitous drop in blood pressure sufficient to produce shock (occasionally with disastrous results for

the baby), cessation of uterine contractions, and the necessity for frequent resort to forceps.

In my opinion there is no more satisfactory and pleasant type of analgesia in obstetrics than this procedure when it is performed properly without a mishap. However, because of the definite though slight risk of death and the chance of producing a minor or a major complication, continuous caudal analgesia has a limited field of usefulness. It is definitely a hospital procedure and should be used only in those hospitals which have a personnel large enough and sufficiently experienced not only in obstetrics and anesthesia, but also specifically trained in the use of caudal analgesia. Likewise, this personnel must have the time and the willingness to be in constant and vigilant attendance on women who are given this type of anesthesia. Furthermore, apparatus must be available for instant resuscitation and people trained in its use. Because of possible dangers and complications, the trained personnel and apparatus required and the high cost of this form of anesthesia, there is no need to employ it for the average woman in labor. Most of the pains of labor, which are quickly forgotten anyway, can be relieved by less harmful drugs and anesthetics.

IV. Spinal Anesthesia (Spinal Analgesia)

Spinal anesthesia or analgesia is one of the most dangerous of all anesthetic procedures. Statistical reports indicate that spinal anesthesia suffers by comparison with nearly all other anesthetics.

Dealy found that among 16,273 inhalation anesthesias there were seven deaths, or one in 2,325 anesthesias, whereas in the same hospital among 3,193 spinal anesthesias there were also seven deaths, or one for every 456 anesthesias, hence the mortality following spinal anesthesia was five times as high as that which followed the inhalation anesthesias.

The following statistics based on nearly a million surgical cases were published by Henson. Table I shows that spinal anesthesia has the highest incidence of death. Among the deaths under local anesthesia there was not a single one where ½ per cent novocain was used, and only one death where a one per cent solution was used. All the other deaths occurred with higher concentrations which should never be used, or with nupercaine or cocaine.

TABLE I. (ARRANGED FROM HENSON)

ANESTHETIC	NUMBER OF CASES	INCIDENCE OF DEATH
Ethylene	31,426	0 per 100,000
Local	146,970	11 per 100,000
Nitrous oxide	188,820	13 per 100,000
Cyclopropane	12,707	15 per 100,000
Ether	513,560	15 per 100,000
Chloroform	3,842	25 per 100,000
Spinal	91,263	42 per 100,000
Total	988,588	

Table II also shows that spinal anesthesia is more dangerous than most other anesthetic procedures.

The risk of death is not the only serious drawback of spinal anesthesia. The incidence of pulmonary complications in high spinal anesthesia is at least as great as after inhalation anesthesia. There are a number of reasons for this, including inhibition of the depth and force of respiratory movements during and after operation, increased viscosity of the secretions of the tracheobronchial tree, and the tendency of the patient to remain immobile after operation.

TABLE II. (ARRANGED FROM TRENT AND GASTER)

ANESTHETIC	NUMBER OF ANESTHESIAS	ANESTHETIC DEATHS	NUMBER PER 1,000 ANESTHESIAS
Local	13,151	0	0
Ether	14,724	6	0.407
Nitrous oxide	6,705	2	0.295
Nitrous oxide with ether	2,175	2	0.919
Cyclopropane	5,744	4	0.691
Spinal	5,436	6	1.10
Spinal with supplement	930	2	2.15
Total	54,128	27	0.498

A toxic effect on the spinal cord and the spinal nerve roots may follow spinal anesthesia. This may be manifested both clinically and pathologically. Davis, Haven, Givens, and Emmett injected the most commonly used spinal anesthetics into the dural sacs of dogs and observed the following changes: a varying degree of inflammatory reaction in the leptomeninges; changes in the ganglion cells of the gray matter of the cord; swelling and fragmentation of the axis cylinders, and signs of degenerative changes in the fiber tracts of the cord. Myelitis and meningitis may result from an infection carried in with the needle or solution, but they may also occur in the presence of a generalized infection that tends to localize at the site of the lumbar puncture. There may be early and temporary effects such as headaches and mild paralysis of the oculomotor and abducens nerve. Late effects may appear months afterward.

Frequently there is a pronounced fall in blood pressure, which may be accompanied by vomiting, restlessness, pallor, cold sweat, weak pulse, shallow respirations, and sometimes unconsciousness. The uterus may fail to relax when this becomes necessary. In more than half the cases high spinal anesthesia retards labor, necessitating operative intervention. This is most likely due to abolition of the sensory phase of the sensory-motor reflex, which normally brings the voluntary muscles into action.

After the drug has been injected into the spinal canal it is beyond control and, if alarming symptoms appear, the cause cannot be removed. This is probably not true when hyperbaric solutions are used. Spinal anesthesia is hazardous in women with anemia and cardiac decompensation. It cannot be used in cases of shock from intraabdominal hemorrhage, abruptio placentae, or other causes.

In spite of some enthusiastic reports on the use of spinal anesthesia in obstetrics, particularly for cesarean sections, a review of the literature should easily convince one that spinal anesthesia is the most dangerous of all anesthetics for pregnant women. In Franken's collected series of 2 088 cesarean sections performed under spinal anesthesia, there were fifteen deaths, or one in every 139 cesarean sections. This is contrasted by Franken with an incidence of approximately one death for every 3,600 operations performed under spinal anesthesia in nonpregnant individuals. Hence, the death rate among the cases of cesarean section was twenty-six times as high as among the nonpregnant patients. Franken attributes the increased death rate in gravid women to two factors: If uterine contractions are present and not relieved by analgesics, the spinal anesthetic may be forced up to the medulla oblongata. Second, the characteristic circulatory changes in pregnancy and the effects of spinal anesthesia on the circulation combine to become particularly dangerous.

Most of the enthusiastic advocates of the use of spinal anesthesia in obstetrics who have been fortunate enough to have had no fatalities have had "near deaths" which have given them anxious and terrifying moments, even

though these moments were brief. Perhaps the recent tendency of confining the anesthetic to the lower regions of the body, the use of smaller doses, the employment of continuous spinal anesthesia and hyperbaric solutions (Sise) which are more controllable will prove safer. But in my opinion it is not justifiable to employ the customary manner of administering spinal analgesia for the delivery of a baby which, after all, is a physiologic and normal function. One may take risks occasionally for men and women who require serious surgical operations, but there is seldom need to subject obstetric patients to the extra hazards of spinal anesthesia, particularly because there are safer methods of anesthesia and analgesia.

V. Local, Infiltration Anesthesia

Practically all surgeons will agree that the safest anesthesia for persons with serious ailments (such as respiratory infections, nephritis, hypertension, severe anemia, diabetes, and other illnesses) is local, infiltration, or block anesthesia. If local anesthesia is the safest for sick individuals, it seems reasonable to conclude that it is also the safest for all who require surgery. As far as I know, there has been no report of the death of a pregnant woman, delivered vaginally or by cesarean section, for which direct infiltration anesthesia with ½ per cent procaine hydrochloride was believed to be the cause. This cannot be said for any other type of anesthetic. Why, then, is not local anesthesia used more frequently than it is in obstetrics? I believe the reasons for this are that most obstetricians are satisfied with the results of inhalation, caudal and spinal anesthesia, in spite of the fatalities and complications which occur. Another is a disinclination or laziness on their part to make use of local anesthesia because they believe that special skill or knowledge is required. This much is certain: nearly everyone who learns the simple technique of giving local anesthesia and uses it a few times becomes enthusiastic about it. Evidence of this is the constantly increasing number of publications on the subject. Further evidence of the fact that direct, infiltration anesthesia can be used extensively is afforded by the figures of the Chicago Lying-in Hospital at which 60 per cent of all the cesarean sections are being performed under local anesthesia and in an additional 15 per cent local and inhalation anesthesia are combined. To date there have been no maternal or fetal deaths or complications which could be attributed to the local anesthetic (Dieckmann). More impressive proof of how frequently local anesthesia can be used is presented by the statistics of the home service of the Chicago Maternity Service. Parasacral block was used 643 times for major operative procedures, and pudendal block and/or local infiltration was used in 2,323 cases (Tucker and Benaron).

The advantages of local, infiltration anesthesia are as follows:

1. There is practically no mortality resulting from this method. The number of fatalities reported in the literature as having occurred after infiltration anesthesia is extremely small and in most instances the drug responsible for these few deaths was cocaine or high concentrations of procaine hydrochloride.

2. There are no pulmonary complications directly attributable to this procedure. It is of special importance in the delivery of women who have pulmonary disorders such as tuberculosis, bronchitis, asthma, and influenza. It is also an advantage in the delivery of women who have eclampsia and preeclampsia, because these patients are particularly susceptible to pneumonia. One of the chief reasons for the absence of pulmonary complications is because the lungs are well aerated, not only during delivery or operation, but also afterward. Because of the absence of vomiting during and after operation, there is no danger of aspiration pneumonitis except in the rarely encountered sensitive woman.

3. There are no local or general complications. There are only three possible difficulties that may arise. A needle practically always breaks near the hub. Its full length should never be inserted so that, should it break off, it can be extracted readily. The second possible mishap is the injection of the solution directly into a vein. To avoid this, one should, before injecting the solution into any area, always pull up on the plunger of the syringe to see whether any blood is drawn into the barrel of the syringe. If blood is seen, a new area must be selected for the injection. Furthermore, the needle should be kept in constant slow motion while the solution is being injected. The third, though rare, possible complication is an idiosyncrasy to the drug used, resulting in shock. The usual symptoms are pallor, perspiration, decreasing pulse rate, nausea, vomiting, cyanosis, and convulsions.

4. The technique is simple and may be carried out in a home as well as in a hospital.

5. There are no ill effects on such vital organs as the liver, lungs, heart, circulatory apparatus, and central nervous system.

6. No special knowledge is required. The physician himself carries out the procedure, and therefore he is not dependent on another individual.

7. No special aftercare is required, as is necessary after general and spinal anesthesia.

8. The amount of blood lost is almost negligible because of the pronounced decrease of bleeding in the operative field.

9. There is no interference with the action of the uterus, of the abdominal wall, or of respiration.

10. Postoperative symptoms are rare.

11. Patients may take liquids and carbohydrates before, during and after the operation.

12. There is seldom any need to hurry through an operation; thus more attention can be paid to proper suturing.

13. The tissues must be handled gently; this is advantageous to the patient.

14. There is less wound infection, since local trauma is diminished and the patient's general resistance has not been lowered.

15. Local, infiltration anesthesia is the least expensive anesthetic.

16. Asphyxia of the child, in contrast to that which may occur with any inhalation anesthesia, does not occur.

Local anesthesia has a few limitations. It should not be attempted in women who are high strung and are definitely afraid of being awake during an operation; likewise in those who are unruly or uncooperative because of severe uterine contractions. Before local infiltration anesthesia is to be used, the operator should have an explanatory talk with the patient. The latter should be promised that her eyes will be covered so she will not see anything around her, that the conversation she will hear will not be gruesome or diagreeable, that the rattle of instruments and utensils will be reduced to a minimum and, above all, that, if she feels much pain and so desires it, she may have an inhalation anesthetic. The operator should live up to all of his promises or the patient may lose confidence, become hysterical, and demand an inhalation anesthetic. The chain of local anesthesia consists of the operator, his assistants (including physicians and nurses), the patient, and the local anesthetic. The most important link in the chain is the operator himself. He must first of all be convinced that local anesthesia is the safest and simplest of all anesthetics; he must learn the technique, and, above all, must be willing to sacrifice the extra time and physical and mental effort that operations performed under local anesthesia demand.

The following obstetric operations can be performed under local, infiltration anesthesia: Dilatation and curettage for incomplete abortion, therapeutic abortion, hydatidiform mole, missed abortion, spontaneous delivery, episiotomy and repair, repair of recent and old childbirth lacerations, low forceps delivery, classic or cervical cesarean section, before or during active labor, Porro hysterectomy, anterior vaginal hysterotomy (vaginal cesarean section), and abdominal and vaginal sterilization. Breech deliveries, and rotation of occiput posterior presentations may be performed when parasacral is combined with local, infiltration anesthesia.

Effect of Anesthetics on the Baby

Local, infiltration anesthesia has absolutely no deleterious effect on the baby. Likewise, caudal and spinal anesthesia do not affect the baby adversely except in the few cases where there is a precipitous drop in blood pressure. On the other hand, the inhalation anesthetics have been responsible for the deaths of some babies. In most cases it is probable that the analgesic drugs given to relieve the pain of the first stage plus the anesthetic administered for delivery caused the fetal casualties; but inhalation anesthetics by themselves have caused deaths of newborn babies. Inhalation anesthetics are particularly dangerous for premature babies and babies whose mothers have diabetes and other complications.

Summary

I have tried to show that whereas anesthesia is a distinct blessing to women in labor, there are dangers associated with every type of anesthetic except direct, infiltration, or block anesthesia. Therefore, every specialist in obstetrics and every physician who has a large obstetric practice should familiarize himself with the simple technique of local anesthesia. Not all women can be delivered under local, infiltration anesthesia, but there is no doubt in my mind that a more widespread use of this form of anesthesia will reduce both the maternal and the fetal mortality and morbidity.

References

Cleland, J. P. G.: Surg., Gynec. & Obst. **57**: 51, 1933.
Davis, L., Haven, H., Givens, J. H., and Emmett, J.: J.A.M.A. **97**: 1781, 1931.
Dealy, F. N.: Am. J. Surg. **60**: 63, 1943.
De Lee, J. B., and Greenhill, J. P.: The Principles and Practice of Obstetrics, ed. 9, Philadelphia, 1943, W. B. Saunders Company.
Dieckmann, W. J.: Am. J. Obst. & Gynec. **50**: 28, 1945.
Franken, H.: Zentralbl. f. Gynäk. **58**: 2191, 1934.
Gillespie, N. A.: J. Anaesth. **19**: 1, 1944.
Greenhill, J. P.: on Direct Infiltration Anesthesia in Obstetrics, in Lull, C. G., and Hingson, R. A.: Control of Pain in Childbirth; Anesthesia, Analgesia, Amnesia, Philadelphia, 1944, J. B. Lippincott Company.
Greenhill, J. P.: S. Clin. North America **23**: 143, 1943.
Greenhill, J. P.: J.A.M.A. **102**: 28, 1934.
Greenhill, J. P.: South. M. J. **26**: 37, 1933.
Greenhill, J. P.: Am. J. Obst. & Gynec. 19: 613, 1930.
Greenhill, J. P.: J.A.M.A. **90**: 1023, 1928.
Hall, C. C.: J.A.M.A. **114**: 728, 1940.
Henson, C. W.: Anesth. & Analg. **16**: 349, 1937.
Hingson, R. A., and Edwards, W. B.: J.A.M.A. **123**: 538, 1943.
Potter, I.: Personal Communication.
Sise, L. F.: Surg. Clin. North America **15**: 1501, 1935.
Spaid, J. D.: J.A.M.A. **114**: 1392, 1940.
Trent, J. C., and Gaster, E.: Ann. Surg. **119**: 954, 1944.
Tucker, B. E., and Benaron, H. B. W.; on Parasacral, Pudendal and Infiltration Anesthesia in Obstetrics, in Lull, C. B., and Hingson, R. A.: Control of Pain in Childbirth: Anesthesia, Analgesia, Amnesia, Philadelphia, 1944, J. B. Lippincott Company.
Waters, R. M., and Gillespie, N. A.: Anesthesiology **5**: 113, 1944.

THE MANAGEMENT OF OVARIAN TUMORS COMPLICATING PREGNANCY*

HENRY C. FALK, M.D., F.A.C.S., AND IRVING A. BUNKIN, M.D., NEW YORK, N. Y.
(From the Gynecological and Obstetrical Services of Beth Israel, Harlem, and French Hospitals)

TUMORS of the ovary occur most frequently during the childbearing period and their presence is not necessarily a barrier to conception. Löhlein[10] reports 1 in 1,738 cases of pregnancy, and Fleischen[7] cites 5 in 17,832. These figures make for an average of approximately 1 in 2,500, but this is undoubtedly low. The apparent low incidence is due to the fact that many cases are not observed on obstetric services, and therefore are not reported. Today, with the recognized necessity for prenatal care, it is probable that more ovarian tumors will be discovered early in pregnancy. The term "tumors" is used in this discussion to designate any enlargement of the ovary and not in the strict pathologic sense.

Many pregnancies, in the presence of an ovarian tumor, have an uncomplicated course. Frequently the tumor remains undiagnosed.

The most common complications which may supervene during pregnancy are torsion of the pedicle, intracystic hemorrhage, and suppuration.[11, 12] Torsion of ovarian cysts is three times more common during pregnancy than in the nonpregnant state, and is particularly prone to occur during the puerperium because of the free mobility of the uterus. Intracystic hemorrhage is usually associated with torsion, but may occur alone. Suppuration may take place with or without torsion, and invariably manifests itself during the puerperium as the result of lymphatic spread of infection from the uterus.

At term an ovarian tumor may obstruct the entrance of the presenting part into the pelvic inlet, or, when the tumor is situated lower down, it may impede descent of the presenting part through the midpelvis. Besides failure of engagement, with possible rupture of the uterus, there exists the possibility of rupture of the cyst into the vagina, into the rectum, or into the peritoneal cavity.

In view of these potential dangers which ovarian cysts impose upon pregnancy, patients in the childbearing age who have ovarian tumors must be properly categorized so that the appropriate treatment can be selected. They fall into one of four groups:

1. Those who are seeking advice prior to becoming pregnant and in whom, on routine examination, an ovarian tumor is found.
2. The pregnant patient in whom an ovarian tumor is discovered during the first trimester of pregnancy.
3. Those in whom an ovarian tumor is discovered during the second trimester of pregnancy.

*Read at the New York Academy of Medicine, Obstetrical and Gynecological Section, Oct. 22, 1946.

4. Those patients in whom the tumor is discovered at or near term, during labor, or immediately post partum.

The woman who is anticipating pregnancy and presents herself for routine gynecologic examination is a problem of particular interest when an ovarian tumor is found. In the light of our present knowledge of the growth potentialities of ovarian tissues, the advice that all tumors regardless of size or location are best removed cannot be accepted today.

The management of the patient with the single small cyst is usually a source of controversy. Accepting the standard that all enlargements of the ovary 5 cm. in diameter or less are small cysts, one will find that 95 per cent of this group are functional cysts.[13] These cysts are no longer looked upon as part of the complex group of ovarian neoplasms, but simply as enlargements which come about as a result of altered physiological behavior of the ovary.

Only 0.6 per cent of this group of small cysts are malignant, and these as a rule are not found in the childbearing period.

If these facts are borne in mind, each of the patients with a small ovarian tumor must be carefully individualized. The treatment will be guided by the characteristics of the individual small ovarian tumors, a knowledge of their tendency to grow, to undergo torsion, to bleed, to grow bilaterally, or to become malignant. During pregnancy, because of their size, they usually rise out of the pelvis with the growing uterus, and serious mechanical complications during labor are rare.

The patient who has been a sterility problem and in whom all studies are negative, except for the finding of a single ovarian cyst, frequently may become pregnant following removal of a cyst. When possible, enucleation of the cyst, rather than oöphorectomy, is the best procedure.

When single or bilateral dermoids are suspected, surgery is always indicated. Twenty-five to 30 per cent of reported series of ovarian cysts complicating pregnancy were found to be dermoids.[12, 14] This high incidence is not surprising since 85 per cent of all dermoids are found early in the period of sexual activity. They are notorious for complicating pregnancy by torsion, rupture, or suppuration, and should be promptly removed if diagnosed at a prenatal examination.[4, 6] Simple resection of the cysts is best when possible.

The patient with endometriosis frequently has bilateral palpable cysts. She usually does not become pregnant.[5] If she does, treatment is one of expectancy unless disabling symptoms are manifest.

The finding of a single solid tumor of the ovary in the nullipara creates a problem. Regardless of its size, when a solid tumor is suspected, laparotomy and removal of the tumor are indicated. If there is no question about its benignity, simple oöphorectomy should be performed. If the tumor is malignant but has an intact capsule, should the other ovary and uterus be removed? Frequently, the exact microscopic diagnosis cannot be obtained at the time of operation. And it is now recognized that there is not necessarily any relationship between microscopic malignancy and clinical malignancy in ovarian tumors.[15, 16] It must therefore be left to the judgment of the surgeon and to his knowledge of

the potentialities of the tumor as to what his procedure should be. The best procedure would be to incise the other ovary to search for possible involvement. But this does not exclude the presence of microscopic tumor elements.

If brief, then, the consensus is that if the tumor is single and encapsulated, a conservative oöphorectomy is the best procedure in the young nulliparous woman who is desirous of having a child. The radical operation is reserved for those cases which are outside the age of reproductivity, where both ovaries are involved, or where the patient has already fulfilled her task of childbearing.

The ovarian cyst which is discovered very early in pregnancy is a problem of special interest from an endocrinologic standpoint. In human beings, as indicated by many clinical observations,[1, 3, 8, 9] it is noted that the integrity of the conceptus is maintained even with removal of the corpus luteum between the sixtieth to ninetieth days of gestation.

Since the ovarian tumor discovered in the first trimester of pregnancy might contain the corpus luteum, it seems wise to delay extirpation of the tumor to some date when the placenta has definitely superseded the corpus luteum. By the sixteenth week of gestation, oöphorectomy rarely entails difficulty.

An inhalation anesthesia such as cyclopropane is the anesthesia of choice because it is delivered with a minimum of anoxia to the patient. Spinal anesthesia is contraindicated because contractions of the uterus are more apt to follow this type of anesthesia than the inhalation drugs. Postoperatively, the patient should be kept well sedated with morphine or one of the opium derivatives for the first forty-eight hours. At this period of gestation there has as yet been little stretching of the abdominal wall, and no difficulty with the healed incision should ensue at term.

Of course, if early in pregnancy an emergency such as torsion of a pedicle or impaction of the uterus below the tumor occurs, then prompt interference is indicated. Before operating, such a patient should receive progestin (at least 5 mg. intramuscularly each day) in the event that the tumor contains the corpus luteum of pregnancy (Table I).

TABLE I. GROUP OF OVARIAN CYSTS TREATED EARLY IN PREGNANCY

NAME	CLINICAL PICTURE	STAGE OF GESTATION	PATHOLOGICAL FINDINGS	POSTOPERATIVE COURSE
M. S. G-I 18	Signs and symptoms of twisted cyst. Bilateral cysts discovered. Pregnant	5 weeks	Right serous cystoma Left papillary adenocarcinoma	Uneventful Now 7½ months pregnant
L. W. G-I 20	Left upper quadrant pain during fourth month of gestation—ovarian cyst palpable	16 weeks	Left ovarian dermoid	Uneventful Spontaneous delivery at term
L. W. G-I 20	Ovarian cyst discovered during first trimester	16 weeks	Dermoid cyst	Uneventful Spontaneous delivery at term
B. P. G-I 28	Bilateral pelvic masses discovered at fourth month. Right oöphorectomy—resection left cyst	16 weeks	Bilateral dermoids	Uneventful Spontaneous delivery at term

The plan for management of ovarian tumors discovered in the second trimester of pregnancy is not much different. Surgery is indicated as soon as the diagnosis is made. At this point any possible endocrinologic deficiencies do not confuse the issue. Single or bilateral cysts can be removed without difficulty. True, a cyst which by this time has undergone repeated torsion may, because of surrounding peritoneal reaction, be adherent to neighboring structures and the omentum.

The discovery of medium and large cysts during the early part of the third trimester calls for temporizing. The fetus is not yet viable, and operation always carries the risk of premature labor and strain on the abdominal wound. Hence, oöphorectomy is unwarranted unless an emergency arises. At term, its handling will then depend upon the location of the tumor and the age of the patient.

When a cyst is discovered at or near term it presents a somewhat different problem. During labor, in the absence of obstruction, delivery from below may be awaited. The cyst may, however, interfere with engagement of the presenting part into the superior strait, or make for dystocia low in the pelvis. Occasionally it can be dislodged. It is indeed a fortunate event if, after placing the patient in knee-chest or Trendelenburg position, spontaneous passage of the tumor into the abdomen occurs. Attempts at forceful displacement are dangerous because of the possibility of rupture with the dissemination of irritating material (dermoid cyst) into the peritoneal cavity. In the instances where the tumor is immobile, the only treatment is elective cesarean section with removal of the tumor at the same time. If at or near term such a cyst is found riding high in the abdomen alongside of the uterus, one might treat the case expectantly, awaiting delivery from below. The mother is thus saved from a cesarean section, which operation may alter her obstetric course in subsequent pregnancies. Such a case, in the elderly primipara, may be subjected to a cesarean section with oöphorectomy at the same time (Table II).

TABLE II. GROUP OF OVARIAN CYSTS REMOVED AT TERM

NAME	CLINICAL PICTURE	STAGE OF GESTATION	PATHOLOGIC FINDINGS	POSTOPERATIVE COURSE
E. S. G-I 22	Right upper quadrant and right flank pain, seventh month. X-ray showed calcified areas. Cesarean section and right oöphorectomy performed	40 weeks	Right ovarian dermoid with hemorrhage	Uneventful
I. C. G-II 23	Knowledge of ovarian cyst at time of first delivery. Mass now in cul-de-sac. Cesarean section and left oöphorectomy	40 weeks	Dysgerminoma, left	Questionable right-sided ovarian enlargement 1 yr.
G. S. G-I 30	Ovarian cyst discovered during last trimester of pregnancy obstructing pelvic inlet. Cesarean section and oöphorectomy	40 weeks	Dermoid cyst	Evisceration. Died
P. M. G-I 20	Knowledge of ovarian cyst throughout pregnancy. Cesarean section and oöphorectomy	40 weeks	Dermoid cyst	Uneventful

The first sign of torsion of the pedicle post partum is an immediate indication for laparotomy. In other cases the ovarian cyst should be removed during the hospital stay because of the possibility of suppuration, especially if a puerperal infection occurs (Table III).

TABLE III. GROUP OF OVARIAN CYSTS TREATED POST PARTUM

NAME	CLINICAL PICTURE	STAGE OF GESTATION	PATHOLOGIC FINDINGS	POSTOPERATIVE COURSE
E. A. G-VIII 24	First diagnosed as acute hydramnios. Ovarian cyst diagnosed after premature induction of labor and delivery of fetus	34 weeks	Ovarian cyst with necrosis and hemorrhage	Died of generalized peritonitis
M. L. G-II 38	Signs and symptoms of peritonitis 3 days postpartum. Ruptured appendix diagnosed	3 days post partum	Bilateral dermoids; one ruptured. Peritonitis	Stormy. Alive and well
B. S. G-II 32	Fever and abdominal pain. Low forceps delivery 17 days previously. Abdominal mass increasing in size. Ovarian abscess diagnosed	4 weeks post partum	Pseudomucinous cyst. Infected and necrotic	Uneventful
M. T. G-II 25	Tumor diagnosed before pregnancy. Spontaneous delivery. Abdominal pain and fever postpartum. Mass in pelvis	3 months post partum	Dermoid cyst with hemorrhage and necrosis	Uneventful

The trend at present has been toward more radical treatment. The size of the tumor often is an important factor in influencing one's judgment. The rules governing extirpation of ovarian tumors in the nonpregnant patient should apply just as well to the ones which complicate pregnancy. In fact, in pregnancy their removal is even more urgent. Solid tumors and bilateral tumors, because of their frequent association with malignancy, should be promptly removed. Bilateral ovarian dermoids can be readily shelled out and small amounts of ovarian tissue which usually sustain ovarian function can be left.

It is stated in the literature that bilateral dermoids complicating pregnancy are rare. Of the 12 cases reported here, seven were found to be dermoids, and in two instances they were bilateral.

The cases considered in this presentation were from the gynecologic and obstetric services of the Beth Israel, French, and Harlem Hospitals in New York City. In some of these cases it was not within the province of the authors to prescribe the therapy. Hence, the management of the case may not correspond with our above outline.

Summary

1. Ovarian tumors are tumors of the childbearing period and may thus complicate a pregnancy.

2. The presence of an ovarian tumor is, as a rule, no barrier to conception.

3. Dermoid cysts are commonly found complicating pregnancy.

4. Torsion, intracystic hemorrhage, and infection are the commonest complications during pregnancy. Torsion and infection are most frequent during the postpartum period.

5. The small ovarian cyst (5 cm.) is usually one of the group of functional cysts and is rarely a cause for concern before or during pregnancy. Larger cysts should be removed when discovered in the nonpregnant patient.

6. All tumors suspected of being solid tumors of the ovary must promptly be inspected. Cases of bilateral ovarian tumors must also be promptly submitted to surgery.

7. Instances of removal of both ovaries during the second and third month with no interruption of the coexisting pregnancy have been reported.

8. The medium-sized and larger ovarian tumors discovered at the onset of gestation may be removed safely during the first trimester of pregnancy under general anesthesia, preferably cyclopropane.

9. Ovarian tumors discovered during the second trimester of pregnancy should be removed at that time. In the elderly primipara, it may be advisable to delay oöphorectomy until term, at which time cesarean section may be done.

10. The cyst which makes for a dystocia problem at term should be removed at the time of the elective cesarean section.

11. Where the ovarian cyst is discovered at term and delivery of the fetus through the natural passages is imminent, the ovarian cyst should be removed soon after delivery in view of the potenial danger of torsion and infection.

12. All the criteria which influence the handling of ovarian tumors in the nonpregnant apply equally as well to the pregnant patient.

13. Twelve cases of ovarian cysts complicating pregnancy are reported—seven were dermoids, two of which were bilateral.

References

1. Ask-Upmark, M. E.: Acta obst. et gynec. Scandinav. **5**: 211, 1926.
2. Berkely, C., and Bonney, V.: Obstetrical Practice, ed. 3, Philadelphia, 1921, P. Blakiston & Co., p. 197.
3. Douglass, M.: Surg., Gynec. & Obst. **52**: 52-55, 1931.
4. Doyle, F. B., and Daversa, B.: AM. J. OBST. & GYNEC. **43**: 1045-1047, 1942.
5. Dreyfuss, Martin L.: AM. J. OBST. & GYNEC. **39**: 95-99, 1940.
6. Falsia, A., and Viggiano, S.: Semana méd. **1**: 167, 1931.
7. Fleischen-Zeittschr. f. Geburtsh. u. Gynäk., Bd. 29.
8. Fränkel, L.: Arch. f. Gynäk. **68**: 538, 1942.
9. Jones, H. W., and Weil, P. G.: J. A. M. A. **111**: 519-521, 1938.
10. Löhlein, H. C. A.: Gynakologische Tagesfragen, Nach Beobachtungen in der Giessener Universitaets Frauenklinik, Wiesbaden, Bergmann, 1890.
11. Lynch, F. W.: California & West. Med. **35**: 415, 1931.
12. McKerron, R. J.: Pregnancy, Labor, Child-bed, with Ovarian Tumor, London, 1903, R. Rebman.
13. Miller, M. F., and Willson, J. R.: New York State J. Med. **42**: 1851, 1942.
14. Peusch, P., and Vanverts, J.: Rev. franç. de med. et de chir. **10**: 243, 1913.
15. Taylor, Howard C., Jr.: AM. J. OBST. & GYNEC. Vol. 40, page 566, 1940.
16. Taylor, Howard C., Jr.: Newer Concepts of Ovarian Tumors. Proceedings of the First American Congress on Obstetrics and Gynecology, pages 32-36, 1939.

SINISTROPOSITION: A STIGMA OF RELATIVE INFERTILITY

ROBERT T. FRANK, M.D., NEW YORK, N. Y.

THE evaluation of fertility is a complex problem. It involves the study of the potency of the male partner, an as yet not fully understood factor of mutual compatibility, and a study of the woman. The investigation of the female must cover not only the mechanical factors of permeability of the passages, but also the endocrine status, normal and pathologic. Included in this phase of the investigation is the hereditary and acquired "constitution." This factor, too often, is not given sufficient consideration in the general estimate. I have repeatedly[1-3] drawn attention to characteristics which distinguish the less fertile groups, some of which are general, others local. Among the latter I have quite recently[3] recognized a previously undescribed malposition of the uterus, which upon further study appears to be of real significance in the evaluation of fertility in a given individual.

This stigma which I have called "sinistroposition" of the uterus I regard as a stigma of relative infertility. In order to obtain further clarification, I have searched my private records covering the last two years and have studied and analyzed the case histories in which sinistroposition was found. Among these histories there were a few patients who had been observed over the course of years and in whom, for reasons to be discussed later, it was noted that sinistroposition had developed, usually while under observation. I call this type secondary or acquired sinistroposition, in contradistinction to the primary congenital form.

The uterus in these patients is situated to the left of the median line, in most instances cervix and body being in contact with the tissues of the left pelvic wall. The left parametrium is found to be short, the right one correspondingly elongated. The right adnexa are long, the ovary usually in its normal position. The left adnexa in the primary cases are above the fundus and close to the left pelvic wall (Fig. 1).

In all, 83 patients fell into the category of sinistroposition. Of these, 70 are classifiable as primary and 13 as secondary in type.

Primary Sinistroposition

Of the 70 primary conditions, 38 were married, but eight of these couples had practiced contraception throughout their married life. Consequently 30 could be considered from the point of view of fertility or infertility. Of the 30, only one had had children (twins). Four claimed to have had spontaneous abortions, but all of these were early and none of these could be positively identified as antecedent pregnancies. Of the 30 patients, 19 consulted me because of sterility. The other 11 had various complaints, none of which were characteristic.

2 had primary amenorrhea
7 had menorrhagia metrorrhagia
1 had dyspareunia
1 had femoral hernia

The remainder of these patients were unmarried, 32 in number. Seven of these were adolescents, under 17 years, while six were between the age of 40 and 46 years. These patients consulted me for various complaints.

Menorrhagia and metrorrhagia	7
Amenorrhea	4
Irregular menses	6
Hirsuties	2
Dymenorrhea	2
Grave's disease	2
Abdominal pain	3
Overweight	2
Lumpy breasts	1
Pseudo adrenal cortical syndrome	1
Question of pregnancy	2

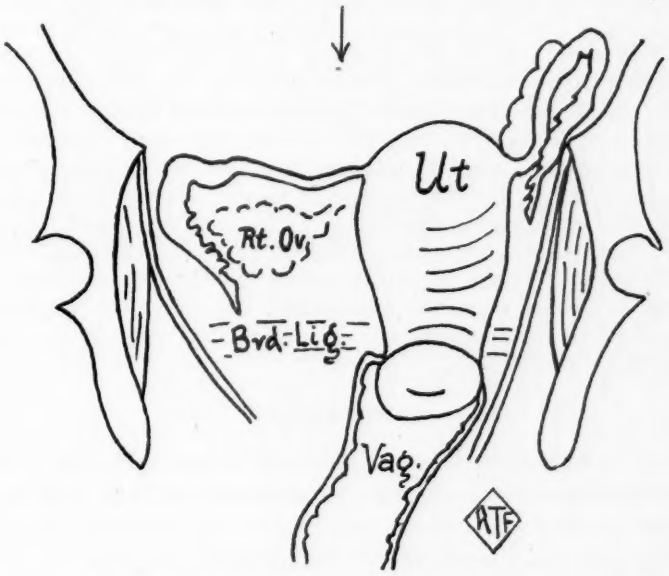


Fig. 1.—Schematic cross section of pelvis showing palpatory findings in sinistroposition of the uterus. Arrow indicates median line.

In my examination I found that 38 of the uteri were either hypoplastic or definitely infantile. In spite of this fact, only 28 of the patients suffered from any dysmenorrhea, and in only two was this actually the major complaint. Another rather striking finding was that in the entire group there were only four retroversions. In the remaining 66, the uterus was anteflexed. Another rather striking feature was that in only two patients were small fibroids noted. As a group, the patients showed a diminution of basal metabolism, the readings being mainly between –11 and –28 per cent, in the 10 cases in which this test had been made. There were two cases of hyperthyroidism.

On the whole, other endocrine stigmas were not noted in excess to what one finds in an unselected group of patients. There were a few eunuchoid individuals, a few in whom constitutional growth disturbances had occurred, but, in the main, the constitution and build were average normal.

To sum up, the impression made by the group of primary sinistroposition was that this local finding must be considered a congenital malformation which, for as yet unexplained reasons, is encountered mainly in individuals who are or will prove sterile or in the less fertile group. I have no explanation for the de-

velopment of this position of the uterus, although it is noticeable that even in normal individual marked filling of the lower sigmoid loop and rectum crowds the uterus to the left. For this reason, if any suspicion as to a temporary displacement of the uterus existed, these women were re-examined repeatedly after thorough emptying of the large bowel. However, in not one case of the series was the displacement due to an overloaded rectosigmoid. If one's attention is once directed to sinistroposition, one will automatically register these patients subsequently.

Secondary or Acquired Sinistroposition

Thirteen patients were grouped as secondary or acquired sinistroposition. This was done particularly in patients in whom the malposition had developed while under observation. In one patient, 54 years of age, the condition did not develop until after the menopause. This patient had been married twenty-seven years and had never become pregnant. In two younger patients on whom I had performed myomectomies, the malposition developed after operation, evidently due to postoperative contractions. In two patients who had never been pregnant, the condition was noted after operation for removal of left ovarian cysts. In four patients the displacement occurred after prolonged inflammatory episodes with numerous relapses. In two patients deep cervical scars extending into the parametrium had pulled the cervix close to the left pelvic wall. In two patients who had been observed, respectively, for eight and ten years, the condition developed under observation in consequence of chronic inflammatory trouble. In sharp contrast to the primary group, seven of the thirteen patients had had children, and one had had repeated abortions. In four, the malposition can be definitely ascribed to the consequence of pregnancy (two deep tears; two postabortal inflammatory episodes).

Summary

From these observations it seems justified to conclude that primary sinistroposition is a developmental stigma characteristic of less fertile females. In evaluating the fertility of a given individual, the presence of sinistroposition should be taken into consideration in arriving at a prognosis.

References

1. Frank, R. T.: Surg., Gynec. & Obst. 45: 189, 1927.
2. Frank, R. T.: Endocrine Aspects of Gynecology, New York, 1931, Nelson's Loose Leaf Surgery, Thomas Nelson & Sons, Chap. XX, p. 461.
3. Frank, R. T.: J. Mt. Sinai Hosp. 12: 5, 1945.

1035 Park Avenue.

THE CAUSES OF DEATH IN CANCER OF THE CERVIX UTERI

RUSSELL R. DEALVAREZ, M.S., M.D., F.A.C.S., PORTLAND, ORE.
(From the Department of Obstetrics & Gynecology, University of Michigan Hospital)

YEAR after year cancer has been responsible for more and more deaths, until, in most States, it ranks among the first three causes of death. In approximately 25 per cent of the women dying from this disease, the lesion is located in the female genital tract, with the cervix as the primary site of the neoplasm in 65 per cent. Unlike most fatal diseases, carcinoma of the cervix per se is rarely the immediate cause of death, most deaths in these cases being due to changes secondary to the original neoplasm. Because very little has been written on this subject and in order to determine just what these causes are, a study was made of the records of 55 patients dying with cancer of the cervix at the University of Michigan Hospital during the past ten years. Complete autopsies, with microscopic examination of all tissues and glands, form the basis of this report.

Symptoms

The most prominent initial symptom among these women had been vaginal bleeding, starting as intermenstrual or postcoital spotting, but gradually progressing in severity. Bleeding persisted and increased to be classed as actual hemorrhage in 71 per cent. Only two patients had no vaginal bleeding. Pain, as a primary complaint, was relatively infrequent, but when it was present it usually occurred in patients in whom the disease was very far advanced.

Type of Malignancy

As indicated in Table I, squamous cell carcinoma of the cervix was the most common type, occurring in 92 per cent. Thirty-eight patients presented medullary squamous cell carcinoma, while eight patients showed the cornifying squamous type.

TABLE I. TYPE OF MALIGNANCY.

Squamous cell	52
Medullary	39
Cornifying	8
Unclassified	5
Adenocarcinoma	2
Sarcoma	1

Associated Diagnosis

In evaluating these patients' records to determine whether or not death was attributable to related medical disease, it was found that no deaths could be directly attributed to an associated medical diagnosis, except in one patient with primary carcinoma of the gall bladder with extensive remote metastases. In this patient the cervical lesion was completely healed and showed no evidence of residual involvement at the time of autopsy.

Clinical Grouping

All patients admitted to our service with carcinoma of the cervix are grouped clinically according to the classification of Miller and Folsome reported in 1938 and their revision of 1945. Eighty-four per cent of this group of 55 patients revealed definite clinical evidence of extension into the parametria, and were therefore in a markedly advanced stage of their disease at the time of admittance.

TABLE II. CLINICAL GROUPING. (U. OF M. CLASSIFICATION.)

	AT TIME OF ADMITTANCE	AT TIME OF DEATH						
		I	II	III	IVa	IVb	IVc	UNCLASSIFIED
Clinic Group I	0							
Clinic Group II	1				1			
Clinic Group III	8			2		4	2	
Clinic Group IVa	25				18	1	6	
Clinic Group IVb	14					12	2	
Clinic Group IVc	4						4	
Unclassified	3							3

The more extensive the clinical involvement, the greater the incidence of interference with vital mechanisms of the urinary tract or alimentary canal. Such interference occurs because the structures carrying on these mechanisms are in the path of spread.

The factors responsible for morbidity were commonly those causing death (Table III). Most patients presented complaints referable first to the urologic tract and second to the gastrointestinal tract.

TABLE III. MORBIDITY.

Urologic	
Secondary to obstructing carcinoma	31
Secondary to invading but non-obstructing carcinoma	5
Gastrointestinal	
Intestinal obstruction	10
Terminal ileitis	2
Irradiation colitis	2
Primary gallbladder carcinoma	1
Pulmonary, from metastatic carcinoma	7
Peritoneal	
Peritonitis	8
Pelvic abscess	6
Neurologic	5
Acidosis	2
Cerebral	2
Hemorrhage	2

Causes of Death

In only one case was the cause of death so obscure as to escape explanation. In 40 per cent death was due to genitourinary invasion and/or obstruction. In most of the patients with ureteral obstruction there was also clinical evidence of pronounced urinary tract infection. In most instances obstruction was due to circumscribed, circumferential infiltration and constriction of the ureter. The occlusion, sufficient to cause death, occurred as a result of either periureteral lymphatic invasion by carcinoma cells in the retroperitoneal lymph node chain or by actual invasive spread of carcinoma into the urinary tract itself. With

this obstruction, naturally stasis, hydroureter, and hydronephrosis developed, and, on this basis, secondary infection. The temperature curves of these patients were of a characteristically septic type. When blood cultures were performed among the patients with this type of febrile course, they were repeatedly negative.

Unless there was clinical evidence of infection or destruction due to infection or hydrostatic changes in the urinary tract, supported by the findings on microscopic examination, the diagnoses of pyelonephritis and infected hydronephrosis were not made.

TABLE IV. CAUSES OF DEATH.

Unknown	1	
Urologic		
Uremia from ureteral obstruction	11	40%
Pyelonephritis from ureteral obstruction	10	
Pulmonary		
Pulmonary edema	8	31%
Pneumonia from metastases	7	
Pulmonary embolism	2	
Gastrointestinal		
Intestinal obstruction	5	13%
Perforation of bowel by carcinoma	2	
Peritonitis	5	
Primary gallbladder carcinoma	1	
Cardiac decompensation	1	
Spontaneous abdominal ureterostomy	1	
Hemorrhage	1	

Uremia was the most common cause of death. In practically all cases renal function studies corroborated the diagnosis and supported the pathologic findings. In most of the cases, microscopic examination showed a severe degree of renal deterioration and destruction. Patients in impending uremia or with pronounced degrees of urinary tract infection, in our experience, have not been greatly benefited from repeated ureteral dilatations in an attempt to overcome their ureteral obstruction. Even though ureteral catheterization could be performed readily, pyelography frequently revealed definite ureteral constriction with dilatation above this point. It is for this reason, plus the fact that ureteral tone and amplitude of contraction were lost, that dilatation of the constricted ureter was invariably unsuccessful in relieving this common cause of death. During more recent years nephrostomy has been attended by rather dramatic results in the alleviation of the tremendous distention of the kidney pelvis presented by these patients. There have been instances in the last few years where patients in apparently moribund uremia have responded most surprisingly, and almost immediately, to this method of control. Concomitant with this striking clinical improvement, distinct amelioration in these patients' blood chemistry (often to normal) was attained. Nephrostomy should not be attempted until the dehydration and inevitable acidosis have been combated with proper electrolytes and large amounts of intravenous glucose. We have observed instances where the carbon dioxide combining power has been as low as 11 volumes per cent, and the nonprotein nitrogen elevated to 190 milligrams per cent in patients in deep coma. These patients have been so completely relieved with nephrostomy that they are now carrying on normal activity in reasonably comfortable circumstances. The operation has usually been an emergency procedure, but may be, and should be, elective. When thus electively performed, it is attended by relatively no shock and with small danger. The place of permanent cutaneous ureterostomy, in this group, must await further observations.

Death from pulmonary causes occurred in 31 per cent. While moderate pulmonary edema is common as a terminal manifestation of a generalized septic process, none of the patients here presented showed any true evidence of sepsis. At autopsy the eight patients in this category showed evidence of massive pulmonary edema. There were no pulmonary metastases among the patients dying from extensive pulmonary edema.

Among the patients with pneumonia from metastatic carcinoma, there can be no question that death was due to sepsis, since there was found markedly widespread infiltration by carcinoma with associated secondary necrotic and infectious processes in the lung. All these patients showed evidence of extensive damage to the lung parenchyma, and in most of them the process was so advanced as to produce asphyxia and even compression of the lung. While bronchopneumonia is the most frequent picture found in debilitated and aged individuals, the changes in our patients were those of massive lobar pneumonia. Pulmonary embolism occurred in 2 patients while they were receiving deep x-ray therapy; in both death occurred before completion of treatment.

Death from gastrointestinal causes occurred in 13 per cent of our series. This was due principally to intestinal obstruction. The obstruction in all cases was due to direct invasion and involvement of the large bowel by the neoplasm; in no instance was the obstruction due to adynamic causes. Invasion was further exemplified by the occurrence of perforation of the bowel due to spreading carcinoma with resultant generalized peritonitis. Since generalized abdominal carcinomatosis is a relatively infrequent finding in patients with carcinoma of the cervix, intestinal obstruction was usually due to regional pelvic involvement. Most of the bowel obstruction occurred in the region of the rectum and rectosigmoid. This was produced as a result of the spread of the carcinoma out through the leaves of the broad ligament directly to the bowel or from massive carcinomatous involvement of and extension to the retroperitoneal lymph nodes which secondarily compromised the lumen. In one patient treated with radium to the extent of 5,520 milligram hours over a 24-hour period, a noncarcinomatous large bowel obstruction was found.

Peritonitis was responsible for five deaths, or 9 per cent of the entire group of patients. Peritonitis, we feel, occurred in these patients as a direct result of spread of infected and necrotizing carcinoma from the primary site out into the pelvic peritoneum with perforation at that point, as well as by bowel perforation by spreading neoplasm. Spontaneous abdominal ureterostomy occurred as the result of direct invasion and perforation of the ureter by carcinoma in one patient; peritonitis however was the immediate cause of death in this patient.

In only one patient was hemorrhage the immediate cause for death. This patient had been bleeding rather briskly for several months without transfusion and shortly after admittance to our hospital died from a terminal overwhelming hemorrhage as the result of erosion of large vessels by the carcinoma. While hemorrhage is considered to be a common cause of death in patients with cervix carcinoma, this was not true in our series.

It is interesting to note that the patient with primary gall-bladder carcinoma died as the result of that carcinoma and its metastases. At the time of autopsy there was no remnant of the cervical neoplasm discernible.

A study was also made to determine the spread of cervix cancer. The route of spread from the primary is not selective, hence any structure along this route may be involved if and when the extension process becomes massive enough.

The genitourinary system was the most commonly affected, and the lymphatic system second. The retroperitoneal nodes were the most frequently involved in the lymphatic system. It was found that, in many of the cases where no actual neoplastic involvement of organs could be shown, damage nonetheless

TABLE V. SITES OF METASTASES.

Urinary tract	Bladder	25
	Ureter	24
Gastrointestinal tract	Rectum	16
	Colon	8
Lymphatic system	Retroperitoneal nodes	23
	Iliac nodes	5
	Peribronchial nodes	4
	Supraclavicular nodes	1
	Inguinal nodes	1
Bone	Rib	3
	Pubis	1
	Knee	1
	Lumbar spine	2
	Femur	1
	Cervical spine	1
Parenchymatous organs	Liver	6
	Heart Muscle	2
	Lungs	11
	Kidney	1
	Spleen	1
Serous cavities	Generalized abdominal Carcinomatosis	5
	Pelvic peritoneum	10
	Pleura	2
Muscle	Pectoralis major muscle	3
	Diaphragm	1
	Psoas muscle	1
Miscellaneous	Sacral plexus	2
	Iliac artery	3
	Mesenteric vein (Ca. thrombus)	1
	Breast	1
	Bone marrow	1
None		10

occurred due to involvement of nodes surrounding the organ. In this way indirect involvement of these structures was effected by the spread and growth of metastatic carcinoma in the nodes. The lower urinary tract was the most frequently involved local site of spread, while the most common site for remote spread was the lung. In the organs involved by constriction, we have found that reduction in size of the lumina has been due not only to invasive malignancy into the structure itself but also to the growth of neoplasm in the immediately surrounding area. This is particularly true in ureteral and large bowel obstruction.

In spreading from the cervix, carcinoma progresses through the lymphatic tributaries which drain the pelvic organs back into the general lymphatic circulation and attack or involve any organ in its path of spread. It is due to involvement and invasion in, as well as growth in these paths of spread, that patients die as the result of carcinoma of the cervix and not from the local primary neoplasm, except in the rare case of hemorrhage. Therefore, radium and x-ray therapy in cervix cancer should be directed toward controlling not only the local site, but also to the sites to which the neoplasm will first spread. Gynecologists and roentgenologists today are not concerned alone with the destruction of the primary site but also seek to prevent its spread and invasion. For this reason clinical examination of all patients with carcinoma of the cervix should include a complete physical examination, pelvic examination, rectal and urologic examination. Satisfactory evidence of extension beyond the cervix cannot be elicited without rectal examination. These clinical procedures should be supplemented by routine x-ray study of the chest and bony structures whenever indicated.

Summary

The causes of death in 55 patients dying with carcinoma of the cervix have been reviewed and analyzed.

Ureteral obstruction (40 per cent), pulmonary causes (31 per cent), and gastro-intestinal causes (13 per cent), account for the majority of deaths among patients with cervix carcinoma.

Nephrostomy, cutaneous ureterostomy, palliative colostomy, and shunting bowel anastomoses may not only lengthen life but may also be lifesaving measures. While nephrostomy and ureterostomy have not yet reached perfection, their continued and more frequent use may lead to improved technic.

Every positive therapeutic measure to control these causes of death must be instituted early to further lower a mortality rate that has already been significantly reduced.

520 MAYER BUILDING.

IS TOXEMIA OF PREGNANCY AN ALLERGIC REACTION?

HAZEL A. C. LIN, M.S., M.D., NEW YORK, N. Y.
(From the Reed and Carnrick Institute for Medical Research)

THE cause of toxemia of pregnancy presents a great challenge to medical research. Uremia, bacteria, toxins, faulty metabolism, and endocrine imbalance have all been blamed. In spite of the tremendous amount of work that has already been put into it, the real etiology is still unknown.

The toxemic manifestations occur only during pregnancy and often disappear soon after delivery or upon death of the fetus. This sequence suggests that the cause may be connected with the product of conception. The fetus has been eliminated as the cause of the trouble, since these manifestations also occur in molar pregnancy. Therefore, the placenta itself has for a long time been looked upon as the source of all the troubles.

The placental aspects have been attacked from all angles. Those workers who advocated hormonal imbalance have reported divergent findings. Smith and Smith[1-3] reported high gonadotrophic and low estrogenic levels in toxemic patients. Their theory was substantiated by Anselmino,[4] Rakoff,[5] and White and co-workers,[6] who discovered excessive gonadotropin in the body fluid of these patients. Taylor and Scadron,[7] however, did not find any significant difference in the hormonal values between normal and toxemic patients. Others found acetylcholine in the placenta and identified it as a potent vasodilator. Hofbauer[16] then put forth the theory that acetylcholine held the delicate balance between the blood pressure stimulating and depressing principles.

Recent interest in antigen-antibody reaction in diseases has been intensified by the work done with anti-kidney serum of Masugi[8, 9] and Smadel.[10-12] Dobrowlski[13] reported that placenta antiserum interruped pregnancy in guinea pigs and rabbits. Seegal and Loeb[14] also encountered the same experience in rats injected with rabbit antiplacenta serum.

It is a common finding of the obstetricians that repeated pregnancies intensify all the symptoms and signs of toxemia of pregnancy. The present experiment was undertaken to find out whether toxemia of pregnancy in rats can be produced by antigen-antibody reaction. A group of virgin albino rats were sensitized by frequent intraperitoneal injections of placental suspension. After a sufficient length of time was allowed for the antibodies to develop, these immunized rats were then allowed to become pregnant. During their periods of gestation, they were tested very carefully for any manifestations of toxemia.

Materials and Methods

Preparation of placental suspensions.—Twenty albino female rats were allowed to become pregnant at fixed intervals so that they could furnish the

placentas according to schedule. The date of copulation was timed by daily vaginal smears. Cesarean sections were performed on these rats one day before term. The placentas were removed aseptically and carefully washed free of blood and ground into small pieces in a glazed porcelain mortar and made up to a 20 per cent suspension with saline solution. Each suspension was used the day it was prepared, as described in the following paragraph.

Preparation of experimental animals.—Ten mature female albino rats weighing 250 to 300 Gm. were kept on Purina dog chow with weekly supplements of yeast, cod liver oil, and hamburger. These rats were obtained from Rockland Farms. These ten rats were given 2 c.c. of the placental suspension intraperitoneally twice a week for five weeks.

These animals were then allowed to have a rest period of five months. At the end of this time they were mated. From their daily vaginal smears their pregnancies were also closely dated.

Lines of investigations.—Evidence of abnormal toxemic pregnancies was determined by careful observation in the urine, blood pressure, and tissue biopsies.

One week after copulation each of these animals was put into a metabolism cage where daily 17-hour specimens of urine were collected. Each specimen was diluted to 50 c.c. with distilled water, and filtered. 0.5 c.c. of this was added to 9.5 c.c. of sulfosalicylic acid. The albumin content was measured by a Klett colorimeter.

The blood pressure readings were taken twice a week from the tail by Grollman's apparatus. The rats were also carefully watched for edema and any other abnormal manifestations during their pregnancies. Biopsies were taken from different organs for microscopic sections.

TABLE I. ALBUMINURIA IN MG. PER TWENTY-FOUR HOURS

RAT NO.	DAYS OF PREGNANCY																DAYS POST PARTUM			
	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	1	2	3	4
1	17	25	22	17	25	27	24	95	49	39	48	33	44	53	55	52	7	0	0	0
2	22	0	32	45	23	40	26	45	49	56	40	37	47	42	49	59	14	12	4	0
3	39	59	72	7	10	27	29	53	45	43	24	39	29	39	59	72	7	0	0	0
4	19	22	22	20	20	20	55	50	36	21	36	23	39	59	52	60	12	0	0	0
6	22	22	26	41	27	29	59	56	58	32	29	32	34	52	27	59	12	13	0	0
7	13	22	25	25	19	25	14	61	35	38	27	26	45	40	36	47	9	5	5	0
8	20	0	24	27	20	25	27	51	50	36	44	36	40	44	51	59	5	5	0	0
10	49	55	51	27	24	33	30	15	27	20	50	30	39	40	34	34	13	0	0	0

Results.—A definite albuminuria developed which, though not heavy, was significant. The urine specimens of this group of animals were frequently tested during the five months prior to their pregnancies, and all during that period were protein free. Furthermore, the albuminuria disappeared quite rapidly during postpartum observation.

Blood pressure studies.—To obtain an accurate reading the rats were heated in an electric cradle to obtain a general hyperemia. The tail was then inserted into a mercury and water cuff. The blood was squeezed away from the tail with the mercury manometer pressure, and the first return of the pulse was registered by the rise of the water manometer as the returning volume of the blood filled the tail.

The normal blood pressure of this group of rats was between 110 to 130 mm. of mercury. As can be seen by the above chart, their blood pressure was definitely raised.

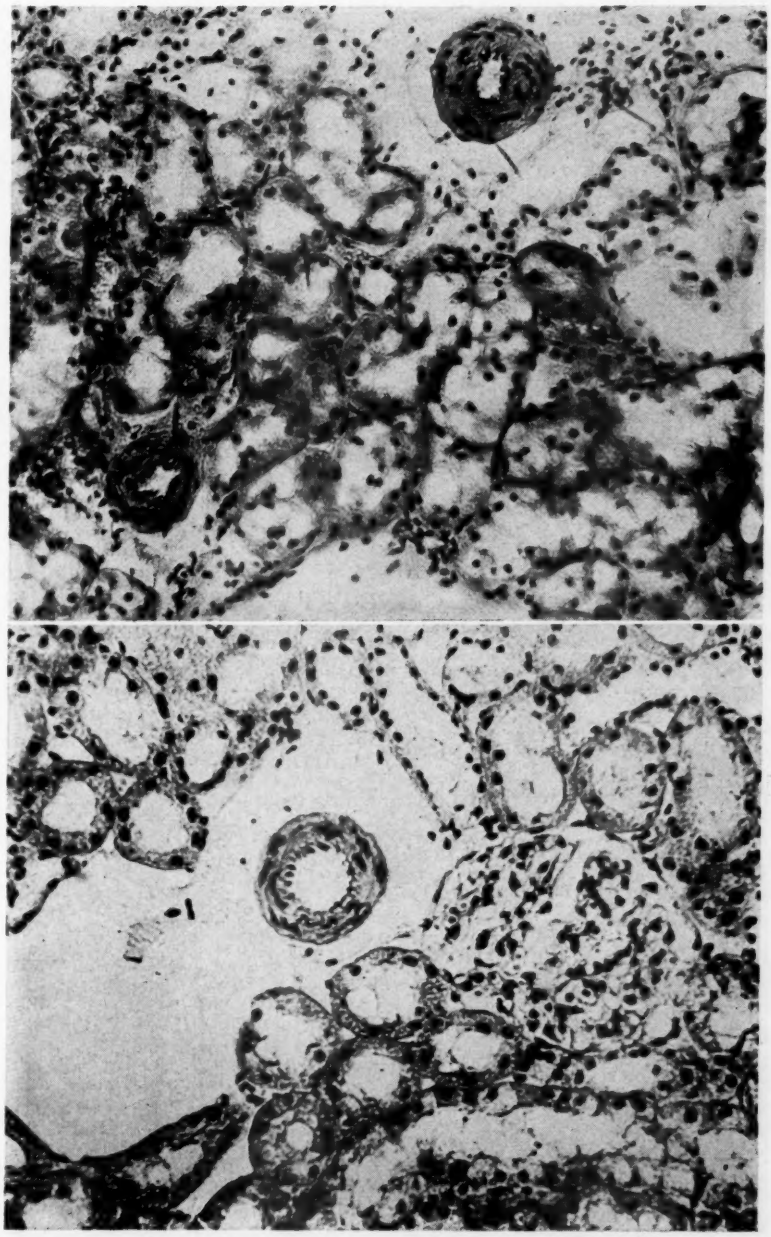


Fig. 1.—Kidney tissue obtained by biopsy three days postpartum from rat No. 4. Note the thickening of the walls of the two arterioles and the reduction of their lumens. The outer circumference of the larger arteriole measured four microns.

Fig. 2.—Kidney tissue obtained by biopsy three days postpartum of a control litter mate of rat No. 4 which had no previous treatment of placental suspension. Note the normal thickness of the wall of the arteriole. The outer circumference of this arteriole also measured four microns.

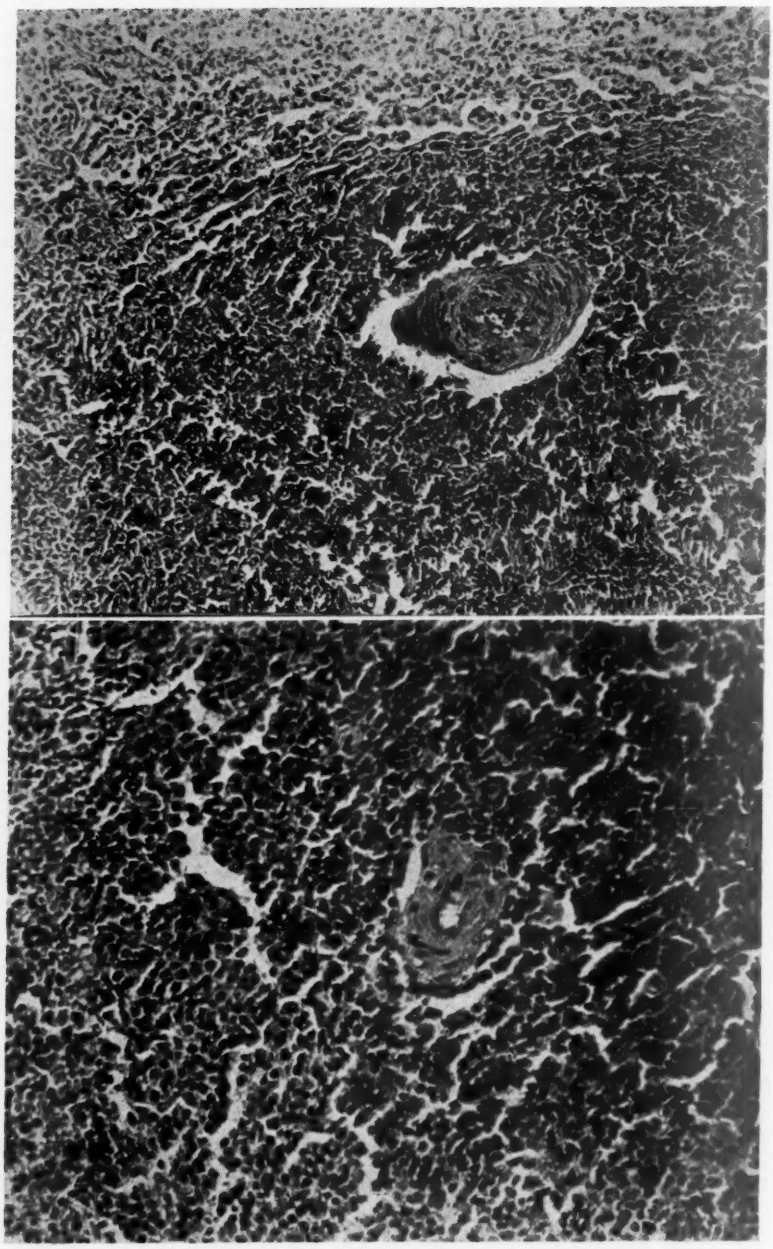


Fig. 3.—Spleen tissue obtained by biopsy from rat No. 8. Note the great thickening of the wall of the arteriole.

Fig. 4.—Pancreas tissue obtained by biopsy from rat No. 2. Note the great thickening of the wall of the arteriole.

TABLE II. BLOOD PRESSURE

RATS	FIRST WEEK	SECOND WEEK	THIRD WEEK
1	145/150	145/145	170/175
2	160/160	165/160	185/180
3	140/140	145/140	140/140
4	110/115	120/125	125/120
6	170/165	160/160	175/160
7	110/130	155/150	160/165
8	150/155	160/150	150/155
10	135/140	140/140	160/165

Two rats had ascites which was proved by paracentesis. One rat had convulsions on two occasions while being heated in the electric cradle. No other abnormal symptoms were observed. All rats carried their pregnancies to term. Six of them had their litters born normally, while the other two had stillborn pups.

Pathology.—Biopsies were taken from the kidneys, spleen, pancreas and liver of all these rats. Sections showed one striking consistent result, i.e., arteriolosclerosis. Some glomerular tufts were ischemic and the basement membranes thickened. (See Figs. 1, 3, and 4.)

Conclusion

A condition closely simulating toxemia of pregnancy with albuminuria, hypertension and edema was produced in rats by sensitizing them against placenta protein before they became pregnant. The most important pathological lesions were found in the arterioles. The walls became greatly thickened and the vascular lumen correspondingly narrowed. There was in the kidney some thickening of the basement membrane of Bowman's capsules as well as ischemia of the glomerular tufts. This pathology corresponds closely to the early lesions in the human toxemia of pregnancy. Wong and Pillot[15] has reported that the earliest sign of toxemia of pregnancy is spasm of the arteriolar wall and the narrowing of its lumen which can be observed in the eye grounds.

The findings in this preliminary experiment suggests that toxemia of pregnancy might be an allergic reaction of the patients to the placental proteins.

References

1. Smith, G. V., and Smith, O. W.: AM. J. OBST. & GYNEC. **38**: 618, 1939.
2. Smith, G. V., and Smith, O. W.: Surg., Gynec. & Obst. **39**: 405, 1940.
3. Smith, G. V., Smith, O. W., and Schiller, S.: J. Clin. Endocrinol. **1**: 461, 470, 1941.
4. Anselmino, K. J., and Hoffmann, F.: Ztschr. f. Geburtsch u. Gynäk. **114**: 61, 1936.
5. Rakoff, A. E.: AM. J. OBST. & GYNEC. **38**: 371, 1939.
6. White, E. P., Titus, R. S., Joslin, E. P., and Hunt, H.: AM. J. OBST. & GYNEC. **198**: 482, 1939.
7. Taylor, H. C., Jr., and Scadron, E. N.: AM. J. OBST. & GYNEC. **37**: 963, 1939.
8. Masugi, M.: Japan Path. Soc. **21**: 329, 1931.
9. Masugi, M.: Beitr. Path. Anat. u. Allg. Path. **92**: 429, 1933-34.
10. Smadel, J. E.: J. Exper. Med. **64**: 921, 1936.
11. Smadel, J. E.: J. Exper. Med. **65**: 541, 1937.
12. Smadel, J. E., and Farr, L. E.: J. Exper. Med. **65**: 527, 1937.
13. Dobrowlski, M. S.: Bull., Int. Sc. Cracovie **5**: 256, 1903.
14. Seegal, B. C., and Loeb, E. N.: Proc. Soc. Exper. Biol. & Med. **45**: 248, 1940.
15. Wong, A., and Pillot: Chinese M. J. **46**: 1159, 1932.
16. Hofbauer, J.: West. J. Surg. **49**: 615, 1941.

FUNGICIDES FOR VAGINAL MONILIASIS

H. Close Hesseltine, M.D., Chicago, Ill.

(From the Department of Obstetrics and Gynecology, the University of Chicago and the Chicago Lying-in Hospital)

ALTHOUGH a large number of chemicals have been studied for fungicidal qualities,[1-3] a stainless, nonirritating, efficient compound is yet to be discovered. These organisms belong to the medical monilia group, more recently called *Candida albicans* by Jordan and Burrows.[4]

These fungi are found frequently in the intestinal and vaginal cavities without symptoms or evidence of mycosis. Vaginal moniliasis occurs almost always during pregnancy. Exceptions are in patients in which common sugars are used as vehicles for vaginal trichomoniasis therapy, or in postmenopausal individuals on excessive estrogenic therapy. Vulvar mycosis is uncommon except in uncontrolled diabetic patients. These established facts leads to the conclusion that these organisms are opportunists. Woodruff and Hesseltine[5] found the frequency of these fungi organisms in the vagina in pregnancy varied in unselected patients from 14 per cent in the outpatient clinic at the Chicago Lying-in Hospital to 41 per cent among Negro group at the "Stock Yards" dispensary.

The promise of chlorothymol, mercuric chloride, and mercurophen was unfulfilled or irregular fungicidal action on the assorted test strains was observed.[6] Gentian violet has been most widely used, but its bold staining features and unsuitable forms for self-administration, along with an occasional sensitization, was the major stimulus to find a better agent, such as element iodine.[6] Element iodine has an established fungicidal potency but it has not been used because no satisfactory method of application had been worked out.

To arrange selfadministration between office visits tablets of potassium iodate and also potassium iodide were made. Kaolin was used as a diluent to slow up the reaction and give prolonged action of the iodine. The acid in the vagina completed the well-known chemical reaction liberating iodine. By supplying sufficient potassium iodine a dilute Lugol's solution was made in vivo. Moderately good but not ideal results occurred, for infrequently a mild iodine "burn" was found in the vaginal vault. The mild degree of burn was verified by the fact that the patients were free from symptoms. Even though cures were effected this preparation was not an ideal agent for these vaginal mycoses.

Because a patient reported symptomatic improvement of her vaginal mycosis following the use of a contraceptive jelly, it seemed pertinent to investigate the various ingredients of this jelly and also a few other new compounds for fungicidal potency against a medical monilia (No. 6225).

The technique of Hesseltine and Hopkins[2] was employed The test strain was an 18- to 24-hour 5 per cent glucose broth culture. The concentration of the respective chemicals and the vehicle for the compounds are indicated in the table. Equal amounts of the suspended broth culture were placed in the test tubes containing the medicament. Each tube was agitated immediately after the addition of the agent to insure thorough mixing. After five minutes' exposure a loop (size 3) of material was transferred to a petri dish. Sabouraud's agar media was poured immediately and the plates rotated to complete the seeding. Observations were made for several days and compared to control plates. Actually the forty-eight hours' reading were thoroughly reliable. Four plus equaled the control, with graduations down through 3, 2, and 1 plus for decrease growth of organism while 0 means no growth. Final concentrations were one-half of the original.

TABLE I. THE FUNGICIDAL POTENCY OF COMPOUNDS UPON MONILIA CULTURES (6225) IN GLUCOSE BROTH AND IN GLUCOSE BROTH TO WHICH HUMAN SERUM AND CELLS HAVE BEEN ADDED.

	CONCENTRATION PER CENT	VEHICLE	BROTH GROWTH	VEHICLE	CELLS AND SERUM GROWTH
1. Ricinoleic acid	0.75	alc. 95%	−	alc. 95%	−
	2.0	gly. 90%, alc. 10%	+	gly.	−
2. Propyl para hydroxy-benzoate	0.1	alc. 50%	−		+
	1.0	gly. 90%, alc. 10%	−	gly.	
3. Oxyquinoline sulfate	0.025	H_2O	++		
4. Stearic acid	5.0	alc. 95%	−	alc. 95%	+
5. Cetyl alcohol	0.5	alc. 95%	−	gly.	++++
6. Cetyl dimethyl ammonium chloride	0.2	H_2O	+	H_2O	−
7. Cetyl diethyl ammonium chloride	2.0	H_2O	−	H_2O	−
8. Cetyl (di-N-Butyl) ammonium chloride	0.2	H_2O	+	H_2O	−
9. Triethanol amine	0.25	H_2O	++++		
10. Sulfamic acid	0.1	H_2O	+++		
11. Calcium propionate	10.0	H_2O	++++		
12. Sodium propionate	10.0	H_2O	++++		

Alc. = alcohol; Gly. = glycerine; H_2O = water. Final concentration of material is one-half.

Those that held promise were subjected to more rigid test by adding blood cells and serum. It has been demonstrated that 50 per cent to 95 per cent ethyl alcohol has some fungicidal action. It should be pointed out also that ethyl alcohol in these concentrations causes irritation of the vaginal mucous membranes and is unsuitable for this organ. These two factors were eliminated by using glycerine as the sole or major substitute for the alcohol soluble compounds. A mixture of 90 per cent glycerine and 10 per cent ethyl alcohol served as a satisfactory vehicle in instances where glycerine alone was not satisfactory.

It has not been demonstrated that complete killing in five minutes is necessarily the best approach for in vivo application but prompt lethal action has received the most attention. Nevertheless previous tests have had partial confirmation by clinical responses to the in vitro lethal materials.

The three cetyl ammonium chloride compounds and ricinoleic acid stand out in their ability to kill all of the *Conidia*. The concentrations were chosen as current information indicates that they are within therapeutic range. Whether the methyl and butyl cetyl ammonium chloride compound may be used in stronger concentration or whether the diethyl compound would be equally as efficient in greater dilution has not been determined.

According to the conditions of this experiment, ricinoleic acid, cetyl dimethyl ammonium chloride, cetyl diethyl ammonium chloride, and cetyl (di-N-butyl) ammonium chloride hold promise as fungicides for monilia which produce vaginal mycosis. Clinical evaluations are now in progress, using 1 per cent concentrations of the cetyl ammonium chloride compounds.

References

1. Hesseltine, H. C., and Noonan, W. J.: J. Lab. & Clin. Med. **21**: 281, 1935.
2. Hesseltine, H. C., and Hopkins, E. W.: J. Lab. & Clin. Med. **21**: 288, 1935.
3. Emmons. C. W.: Arch. Dermat. & Syph. **28**: 15, 1933.
4. Jordan, E. O., and Burrows, W.: Text Book of Bacteriology, ed. 14, Philadelphia, **1945**, W. B. Saunders Co.
5. Woodruff, P. W., and Hesseltine, H. C.: AM. J. OBST. & GYNEC. **36**: 467, 1938.
6. Hesseltine, H. C.: AM. J. OBST. & GYNEC. **34**: 439, 1937.

THE USE OF GELATIN FOAM SPONGES IN OBSTETRICS AND GYNECOLOGY

ALLAN C. BARNES, M.S., M.D., COLUMBUS, OHIO

(From the Department of Obstetrics and Gynecology, The Ohio State University Medical School)

THE various properties of the recently introduced gelatin foam absorbable sponges have been thoroughly investigated,[1, 2] but their principal clinical application to date has been in the realm of neurosurgery.[3, 4] During the past nine months we have employed these sponges extensively on the gynecologic service of The University and St. Francis Hospitals* in an effort to evaluate their proper clinical application in obstetric and gynecologic surgery.

In their dry state the sponges are crisp, moderately friable wafers. They are moistened by immersing in the desired solution and gently compressing until all air bubbles have been expressed, after which they may be dried by pressing them on gauze pads. The term "sponge" has apparently been prompted by analogy in physical appearance and does not apply to their function. Gelatin foam sponges are not intended entirely to replace gauze sponges at the operating table. Moistened with either saline or a solution of bovine thrombin, however, they provide a valuable means of hemostasis.

In ten patients, purely for experimental purposes, portions of sponge were left in the uterine cavity at the time of curettage. As evidenced by the somewhat malodorous discharge, degeneration began within forty-eight hours and persisted for about ten days. Apparently most of the sponge was lost by discharge rather than by absorption.

The intrauterine use of these sponges, however, is hazardous, and requires an understanding of the mechanism of intrauterine hemostasis. Neither postpartum blood nor menstrual blood is a clotting fraction,[5] and in vitro experiments in this laboratory have indicated that a sponge saturated with thrombin will not cause clotting of these bloods. In this respect they differ sharply from both oxalated and heparinized blood which we have found will clot in vitro after the addition of a portion of thrombin moistened sponge. It must be remembered, therefore, that the use of these sponges to control postpartum bleeding or excessive menstrual flow is without physiologic foundation. There is, indeed, no indication that the formation of a clot in the uterine cavity plays any part in the control of uterine bleeding,[6] and during the postpartum period intrauterine sponges would have the additional potential hazard of preventing adequate contraction of the sinuses of the placental bed.

Perineal and abdominal surgery.—The use of these sponges for hemostatic purposes in both perineal and abdominal surgery has provided us with an

*The gelatin sponges used were generously supplied by the Upjohn Company, who market them as Gelfoam.

instrument of considerable value. The raw oozing surface in the posterior cul-de-sac following the dissection out of endometriosis or old inflammatory diseases is particularly amenable to such management, and we have also employed them following the stripping of the bladder flap from the uterus.

In the postoperative courses of these patients we have noted no febrile reaction of significance which could be ascribed to the absorption of the sponge. On subsequent examinations, no undue scar tissue could be palpated which could be attributed to their absorption. From such follow-up examinations, however, it was our impression that the disappearance of the gelatin was much more rapid than has been reported in the animal, beginning within a day or two after surgery and being complete within one or two weeks. One patient in this series was readmitted four weeks after hysterectomy for emergency surgery of the upper abdomen, and exploration of the pelvis at that time revealed good healing with no evidence of residual from the previously employed (9 cm. by 13 cm.) sponge. In another patient with an inoperable malignant cyst of the ovary, marsupialization was employed, providing us with an opportunity to follow the fate of the sponge left in the cyst cavity. Absorption began shortly after operation, and was complete two weeks later.

From the point of view of hemostasis, it cannot be stressed too frequently that these sponges with anticoagulants do not constitute an alternative to the hemostat. Their fields of application are quite disinct, and to substitute the absorbable sponges for the hemostat or ligature will create far more problems than it will solve. At the operating table we have not been able to observe any great difference in speed of hemostatic effect with or without the bovine thrombin. The gelatin sponges themselves, when saturated in blood or saline, apparently have a coagulative action, and we feel that their proper use is as important as the solution used. The careful pressing out of all air bubbles from the material at the time of moistening, and the maintenance of firm pressure to the sponge for a few minutes after applying it to the tissues are the steps of greatest value in obtaining hemostasis.

Comparative bacteriologic studies in this laboratory indicate that the gelatin can serve as a culture media for organisms. The sponge saturated with blood, however, does not constitute a culture media significantly more favorable than does clotted blood alone, and the hazard is more potential than real.

It has not yet been demonstrated that a raw area covered by an absorbable gelatin sponge corresponds surgically to a peritonealized area. Nevertheless, in about a third of the laparotomies in which they were employed in the posterior cul-de-sac, no peritonealization was carried out. Until further investigations are reported, however, gelatin foam sponges should be used as a substitute for peritonealization with great caution, and only when more standard methods cannot be employed.

Conclusions

1. The use of absorbable gelatin foam sponges in obstetric and gynecologic surgery has been reviewed.

2. The intrauterine use of such sponges with or without thrombin solution for hemostatic purposes is without physiologic basis, and in menstrual or postpartum bleeding is potentially hazardous.

3. The sponges provide an excellent means of hemostasis in the control of oozing areas in pelvic or perineal surgery, whether used with thrombin or with saline. They supplement, but cannot replace, the hemostat.

4. Neither a febrile reaction nor excessive scar formation has been noted in the postoperative course of these patients.

5. The gelatin-foam sponge impregnated with blood provides a potential culture media for bacteria, but not significantly different from that provided by clotted blood.

References

1. Light, R. U., and Prentice, H. R.: Arch. Surg. **51**: 69-77, 1945.
2. Light, R. U., and Prentice, H. R.: J. Neurosurg. **2**: 433-445, 1945.
3. Pilcher, C., and Meacham, W. F.: Surg., Gynec. & Obst. **81**: 365-369, 1945.
4. Light, R. U.: J. Neurosurg. **2**: 414-434, 1945.
5. Barnes, Allan C.: Am. J. M. Sc. **213**: 463, 1947.

SICKLE CELL ANEMIA AND PREGNANCY

JOHN H. HODGES, M.D., AND J. BERNARD BERNSTINE, M.D., PHILADELPHIA, PA.

(From the Department of Medicine and the Department of Obstetrics and Gynecology, Division of Obstetrics, of the Jefferson Medical College and Hospital)

THE infrequency of pregnancy in women with sickle cell anemia is suggested by the fact that to date only 20 cases have been reported.[1-13] This is surprising when, by survey, it is noted that about 8 per cent of Negroes in the United States[14] have the "trait"; that is, they have erythrocytes which are capable of assuming the "sickle" shape; and about 0.2 per cent of Negroes[14a] have, in addition, the clinical entity called sickle cell anemia. This is manifest by episodes of pain in various parts of the body, fever, jaundice, hepatomegaly, chronic ulcers of the extremities, persistent anemia with sickled and nucleated erythrocytes in the peripheral blood, leucocytosis, reticulocytosis and a hyperplastic bone marrow.

Cases of sickle cell anemia and pregnancy may frequently be overlooked clinically, and, for this reason, three additional cases are here reported. Two of these patients had signs and symptoms of central nervous system involvement which occurred immediately following delivery and presented a picture resembling toxemia of pregnancy.

Case Reports

CASE 1.*—B. L., a 23-year-old Negro woman, was admitted to the hospital on Sept. 26, 1944, because of amenorrhea since April 23, 1944, and anemia. She had a history of "pneumonia" recurring since the age of 8 years and occasional attacks of abdominal pain, fever, and chills, with jaundice. On several occasions these attacks were accompanied by periods of unconsciousness. She was short, slight of stature, icteric, and pale. The blood pressure was 90/50. There was a soft apical systolic murmur and an accentuated pulmonic second sound. The uterus was symmetrically enlarged to the level of the umbilicus, and there was slight pitting edema of the ankles.

Laboratory Findings on Admission.—Urinalysis—albumin, 4 plus; occasional granular casts and erythrocytes. Blood count—hemoglobin, 4 Gm. (or 26 per cent); erythrocytes, 1,380,000 per cu.mm.; reticulocytes, 0.8 per cent; platelets, 442,000; leucocytes 11,500; differential count, normal. Nucleated and sickled erythrocytes were present in the blood smear. The erythrocyte fragility tests showed increased resistance. There was hyperplasia of the erythroid elements of the bone marrow. The urea clearance was 40 per cent, with a blood urea nitrogen of 20 mg. per cent. The urine urobilinogen was positive in a dilution of 1 to 100. Roentgenograms showed a thinning of the cortexes of the bones, the heart appeared enlarged in all diameters, and the lung markings were generally increased in intensity.

*The Charlotte Drake Cardeza Foundation performed many of the hematological studies recorded for Cases 1 and 2.

During the next three months the patient received five transfusions of citrated blood, 500 c.c. each, and four transfusions of red cell suspension, 600 c.c. each. The edema of the ankles increased, and the blood pressure rose to 152/92. The membranes ruptured spontaneously on Jan. 22, 1945, after thirty-nine hours of labor. The patient immediately delivered herself of a cyanotic, 3 pound, 12 ounce male infant. After spontaneous delivery of the placenta she complained of headache. The blood pressure was 140/110. She was given 0.01 Gm. of morphine sulfate, subcutaneously. Four hours post partum she had convulsions during which she fell from bed, became unconscious, and was incontinent of urine. Convulsions recurred an hour and one-half later. The retinal veins were distended; the arms and legs were spastic; Babinski's sign was present bilaterally. A spinal fluid study was normal. The impression of the neurosurgical consultant (Dr. Rudolph Jaeger) was " . . . diffuse brain irritation by multiple lesions, probably petechial hemorrhages. . . ." On the following day the blood urea nitrogen was 30 mg. per cent, and the serum uric acid 8.8 mg. per cent. She gradually regained consciousness until on the fourth day she was able to read and write. A week after the convulsions she was free of abnormal neurologic findings, except for involuntary muscular twitches of the face, arms, or legs occurring several times each hour, frequent headaches, and a "hazy memory." The serum uric acid declined to 4 per cent, and the urea clearance to 16 per cent. The electroencephalogram was abnormal, nonspecific type. A year later the electroencephalogram was normal.

The baby fed poorly and died eleven days after birth. Blood counts, platelets, and fragility tests were normal. At no time was sickling present. Autopsy revealed prematurity, subarachnoid hemorrhage, and aspiration pneumonia.

The erythrocytes of the child's father showed no sickling.

CASE 2.—S. M., a 21-year-old Negro woman, was admitted to the hospital Jan. 17, 1940, with amneorrhea since Sept. 20, 1939, a genital sore, and vaginal discharge for three weeks, lower abdominal pains for six days. There was a scar over the left tibia from a chronic ulcer in childhood. On March 9, 1938, she had had an uncomplicated delivery of her first child, a girl (child 1). The blood pressure was 100/60. There was a systolic murmur at the aortic region of the heart. The entire right side of the abdomen was tender, and the uterus was symmetrically enlarged to the level of the umbilicus.

Laboratroy Findings.—Urinalysis—albumin, 1 plus (noncatheterized). Blood count—hemoglobin, 6.9 Gm. (or 45 per cent); erythrocytes 2,770,000 per cu.mm.; leucocytes 8,300 with a normal differential count. There were, however, 547 nucleated erythrocytes to each hundred leucocytes in the blood smear which also contained occasional sickled erythrocytes. The bone marrow showed hyperplasia, especially of the erythroid elements. Cervical and urethral smears were negative for gram-negative intracellular diplococci. The Frei test was negative. The blood Wassermann and Kahn tests were plus 4. A roentgenogram of the chest showed a generalized intensification of the pulmonary markings and enlargement of the cardiac silhouette.

The patient's temperature returned to normal in three days. She complained of pain in the bones of the extremities, and it was noted for the first time that the liver was enlarged. After her discharge from the hospital she received antisyphilitic therapy (bismuth and iodides). Up until the time of delivery she complained of dizziness, blurred vision, nausea, dyspnea, and palpitation. The ankles were edematous.

The onset of labor was at 8:45 P.M. on May 24. The blood pressure was 112/80. Approximately one and one-half hours later she delivered, spontaneously, a 6 pound, 4 ounce female child (child 2). The placenta delivered, intact, ten

minutes later. The uterus contracted well. During the postpartum period of hospitalization the patient's temperature varied between 99° and 100° F., without evidence of infection.

On Oct. 21, 1942, the patient returned, complaining of nausea, dizziness, shortness of breath, blurred vision, palpitation, and continuous abdominal pain. She was pregnant, and the estimated date of delivery was Jan. 8, 1943. Two months later she had a sudden sharp pain in the left hemithorax associated with dyspnea, cough, and white mucoid expectoration. The symptoms gradually subsided with bedrest.

On Jan. 5, 1943, after a labor of fifteen hours, the patient spontaneously delivered a premature-appearing female child (child 3). The following day the patient developed dyspnea, severe pain in the left side of the chest, accompanied by cough and mucoid expectoration. In addition she complained of severe pain in the left leg. The scleras were icteric. There were signs of atelectasis on the left side of the chest posteriorly. The liver edge was two inches below the right costal margin. The sputum showed the usual respiratory organisms (culture) with a negative smear and culture for tubercle bacilli. Leucocytes numbered 53,000 with a normal differential count, but 870 nucleated erythrocytes were counted for each hundred leucocytes. Reticulocytes averaged 40 per cent. The van den Bergh reaction was positive direct with the serum bilirubin 1.5 mg. per cent. A roentgenogram showed cardiac enlargement with an increased density in the lower left lung field. The impression of the hematologist, Dr. L. M. Tocantins, was that the patient had sickle cell anemia with pulmonary infarction. She was discharged, improved, on Jan. 30, 1943.

Children.—

Child 1: At 8 years of age this child had a hypochromic anemia but no evidence of sickling.

Child 2: At 6 years of age examination of the blood showed a normal erythrocyte count with a low color index but no evidence of sickling.

Child 3: At 3 years of age examination of the blood revealed a low color index with sickling present.

(The case histories of these children are to be published in detail, elsewhere.)

CASE 3.—E. W., a 22-year-old primipara, was admitted to the hospital July 10, 1946, because of painful, slightly swollen joints of the extremities. She gave a history of similar attacks occurring about once a year since the age of 12 years. There were systolic murmurs at both the pulmonic and mitral regions of the heart. The blood pressure was 94/52. The uterus was enlarged to about the size of a six months' pregnancy.

Laboratory Findings.—Urinalysis negative. Blood count—hemoglobin, 5 Gm. (or 33 per cent); erythrocytes, 1,890,000 per cu.mm.; leucocytes, 12,000; polymorphonuclear cells, 73 per cent; eosinophiles, 2 per cent; lymphocytes, 20 per cent; monocytes, 7 per cent; and nucleated erythrocytes, 36 per hundred leucocytes counted. Sickle cells were present in the ordinary blood smear. Reticulocytes were 1 per cent. The bone marrow showed an increase in erythropoietic elements. There was 5 per cent retention of bromsulfalein, the van den Bergh reaction was positive direct, and the serum bilirubin was 1.1 mg. per cent with the urine urobilinogen positive in dilution of 1 to 50. The blood urea nitrogen was 8.8 mg. per cent; the urea clearance, 85 per cent; the serum uric acid, 5.8 mg. per cent. Roentgenogram of the chest showed cardiac enlargement, particularly of the left ventricle.

The patient was discharged after receiving three transfusions each containing 500 c.c. of citrated blood, and was readmitted on Sept. 16, 1946, in labor about two weeks before the estimated date of delivery. The erythrocyte count

was 2,500,000 per cu.mm. She received 500 c.c. of citrated blood during labor. The membranes were artifically ruptured and, under spinal anesthesia (50 mg. novocain), a 4 pound, 4½ ounce living male child was delivered by forceps after a labor of about 24 hours. During the prenatal period the highest level recorded for the blood pressure was 134/74. About twelve hours post partum the patient started to complain of severe frontal headache and blurring of vision. The blood pressure at this time was 180/100. The following day it was noted that there was nuchal rigidity, bilaterally positive Kernig's sign, and generalized hyporeflexia. The serum uric acid was 8.8 mg. per cent; serum bilirubin, 1.1 mg. per cent. On the third day post partum the spinal fluid pressure was 470 mm. of water; 22 c.c. of yellow fluid were removed, the analysis of which showed many erythrocytes; sugar, 50 mg. per cent; protein, 30 mg. per cent; Wassermann, negative; and absence of growth on culture.

The patient developed transitory ptosis of the right eyelid with limitation of internal and upward movement of the eyeball and Cheyne-Stokes type of respiration; papilledema was present bilaterally. The liver was enlarged and tender, and the spinal fluid pressure remained elevated. Very slow reduction of this pressure gave much relief from the headache, and the respirations became more regular. At no time did the blood urea nitrogen go above 11 mg. per cent, but six days post partum the urea clearance was 50 per cent. The serum uric acid decreased to 4 mg. per cent. A month post partum the cerebrospinal fluid was normal except for a pressure of 400 mm. of water. By Oct. 20, 1946, there was sufficient clinical improvement to permit the patient to be discharged to the Out-Patient Department.

An electroencephalogram performed at the first admission was normal. One performed ten days post partum was abnormal, but had no definite localizing criteria.

The general progress of the baby was good. Blood counts performed from within twenty-four hours of birth to four weeks of age were normal. Stasis moist preparations made at about 3-day intervals showed sickling for the first time on the twenty-fourth day.

Discussion

These three patients had the typical signs and symptoms of sickle cell anemia. A critical survey of these, along with those previously reported, with pregnancy, focuses attention upon certain prominent features. Sydenstricker,[1] in reporting the first two cases, did not furnish clinical descriptions, so that actually only 21 cases can be reviewed. All but three of the patients were less than 30 years of age, the oldest was 35 and the youngest 16 years. Six died as a complication of pregnancy. Thrombotic phenomena were suggested by the clinical course of ten, seven of these had signs and symptoms of pulmonary infarction, two of cerebral thrombosis, three of thrombi in the legs or vessels of pelvic and abdominal viscera. Nine gave histories of spontaneous abortions, miscarriages, or both. Thirty-two of the pregnancies were reported as having progressed beyond seven calendar months. Twenty-four of these survived, and eight died either in utero, at delivery, or soon afterward. Nineteen of these infants were examined for sickling, and fourteen reported as positive.

The blood pressure was reported in thirteen cases (including the three reported here); seven had hypertension (diastolic blood pressure over 90 mm. of mercury). In Case 1 of this series, there was albuminuria, declining kidney

function, edema of the lower extremities, hypertension, increased serum uric acid, convulsions, and a comatose state; these findings, together with the fact that the patient was a primigravida, strongly suggested that she had eclampsia. It must be noted, however, that she had periods of unconsciousness previous to her pregnancy, apparently as a part of a state of "crisis." In 1940 Hughes, Diggs, and Gillespie[15] described six cases of involvement of the nervous system in sickle cell anemia and reviewed twenty-five cases from the literature. Drowsiness, stupor, or coma occurred in sixteen of these, hemiplegia in fourteen, and convulsions in eight. If this patient had a "crisis" as a complication of her pregnancy, clinical evidence suggests that it involved only the central nervous system. This, too, has been reported. These same authors and Connell[16] have described the presence of thrombi, areas of necrosis, hemorrhage, pigmentation, and vascular intimal proliferation in the brain in sickle cell anemia. Our patient had normal cerebrospinal fluid. In their cases the state of the cerebrospinal fluid was variable and often normal, even in the presence of diffuse cerebral involvement.

In Case 3 hypertension developed within twelve hours post partum, accompanied by blurring of vision, nuchal rigidity, a bilaterally positive Kernig's sign, and elevation of the serum uric acid. Later there were signs suggesting a lesion of or near the circle of Willis. The evidence presented in both Case 1 and Case 3 suggested the presence of cerebral thromboses, hemorrhages, or both.

Both patients of Case 1 and Case 3 had rather acutely declining urea clearance values associated with pregnancy and elevated values for serum uric acid during the period with hypertension and abnormal cerebral signs. According to Dexter and Weiss,[17] a declining urea clearance value is not common in normal pregnancy, but is frequently seen in toxemia. The studies of Schaffer, Dill, and Cadden[18] suggest that the increased uric acid content of the blood in toxemia is due to a decreased renal clearance of uric acid, and postulate that there is not a concomitant rise in urea nitrogen because pregnancy normally lowers the blood urea content. Renal impairment and even uremia may occur in sickle cell anemia.[19]

The evidence strongly suggests that toxemia was present in Cases 1 and 3. In toxemia of pregnancy it is generally accepted that there is spasm of the arterioles.[20] This spasm superimposed on vessels already partially occluded by intimal proliferation may bear an important relationship to the occurrence of signs and symptoms of cerebral vascular blockage.

In Case 2 there was evidence of pulmonary infarction as a complication of pregnancy. Six of the patients previously reported had symptoms and signs, during their pregnancy, which were suggestive of pulmonary infarction. In all three cases there were complications by vascular phenomena, probably thromboses. This is a characteristic of sickle cell anemia, but in these instances it would appear that the tendency, was, in some manner, enhanced by pregnancy.

Summary

1. Three case reports of sickle cell anemia in pregnancy are added to the twenty published cases.

2. Two of these patients presented signs and symptoms of toxemia of pregnancy.

3. In sickle cell anemia with pregnancy vascular phenomena, particularly thromboses, occur frequently. These phenomena may, in these instances, bear an important relationship to the occurrence of, or the severity of, the symptoms of the toxemia of pregnancy.

References

1. Sydenstricker, V. P.: J. A. M. A. 83: 12, 1924.
2. Yater, W. M., and Mollari, M.: J. A. M. A. 96: 1671, 1931.
3. Lash, A. F.: Am. J. Obst. & Gynec. 27: 79, 1934.
4. Richter, O., Meyer, A. E., and Bennett, I. P.: Am. J. Obst. & Gynec. 28: 543, 1934.
5. Sharp, E. A., and Schleicher, E. M.: Am. J. Clin. Path. 16: 580, 1936.
6. Killingsworth, W. P., and Wallace, S. A.: South. M. J. 29: 941, 1936.
7. Lewis, A. W., Jr.: Am. J. Obst. & Gynec. 33: 667, 1937.
8. Sodeman, W. A., and Burch, G. E.: New Orleans M. & S. J. 90: 156, 1938.
9. Page, E. W., and Silton, M. Z.: Am. J. Obst. & Gynec. 37: 53, 1939.
10. Kobak, A. J., Stein, P. J., and Daro, A. F.: Am. J. Obst. & Gynec. 41: 811, 1941.
11. Van der Sar, A.: Revista Policlín. Caracas. 12: 1, 1943.
12. Spivack, M.: Am. J. Obst. & Gynec. 50: 442, 1945.
13. Noyes, R. W.: Am. J. Obst. & Gynec. 52: 469, 1946.
14. Lewis, J. H.: The Biology of the Negro, Chicago, 1942, The University of Chicago Press.
14a. Diggs, L. W., Ahmann, C. F., and Bibb, J.: Ann. Int. Med. 7: 769, 1933.
15. Hughes, J. G., Diggs, L. W., and Gillespie, C. E.: J. Pediat. 17: 166, 1940.
16. Connell, J. H.: J. A. M. A. 118: 893, 1942.
17. Dexter, L., and Weiss, S.: Pre-eclamptic and Eclamptic Toxemia of Pregnancy, Boston, 1941, Little, Brown & Co.
18. Schaffer, N. K., Dill, L. V., and Cadden, J. F.: J. Clin. Investigation 22: 201, 1943.
19. Wintrobe, M. M.: Clinical Hematology, Philadelphia, 1942, Lea & Febiger.
20. Mussey, R. D., Hunt, A. B., and Sluder, F. S.: Am. J. Obst. & Gynec. 45: 224, 1943.

Addendum

A fourth case has been observed since submission of this paper for publication. A 19-year-old Negro primigravida, at term, with sickle cell anemia, delivered spontaneously after eight hours of labor, a 4 pound, 10 ounce male infant (Jan. 21, 1947). The next day she developed signs of bilateral basilar pulmonary atelectasis followed by a nonspecific pneumonitis with slow recovery. The infant's blood did not show sickling. It gained weight slowly, developed diarrhea, and died at the age of two months.

PEPTIC ULCER WITH HEMORRHAGE DURING PREGNANCY AND FETAL DEATH

EDWARD B. LEWINN, M.D., F.A.C.P., PHILADELPHIA, PA.
(From the Frankford Hospital)

THE frequency with which epigastric distress, heartburn, and sour belching are complained of in the latter weeks of pregnancy indicates that there exists functional or organic disease of the upper gastrointestinal tract in a large proportion of gestations. Unfortunately, these symptoms are too often taken as a matter of course by the physician. Gravid women who present manifestations of digestive disease or disorder are rarely studied for the purpose of discovering their precise nature and cause. Sandweiss and co-workers[1] point out that patients admitted to obstetric or gynecologic hospital services are not, as a rule, questioned closely about gastrointestinal complaints. Yet, in a review of the literature, these authors collected 13 instances of death due to hemorrhage or perforation of gastroduodenal ulcer occurring immediately or shortly after delivery, adding one case of their own. Their report is in contrast with the opinion quite generally held that pregnancy has a beneficial influence on pre-existing peptic ulcer. However, there is evidence to show that such a concept is only partially true.

Clinical and experimental investigations point to a probable relationship between endocrine activity and gastric secretion. From a clinical point of view it is to be noted that 80 to 90 per cent of peptic ulcers in adults occur in men; yet, before puberty the incidence is approximately the same in both sexes (Bockus[2]). The relative infrequency of peptic ulcer in women appears to be even more marked during pregnancy. Sandweiss, Saltzstein, and Farbman[3] were able to find only one proved case of chronic peptic ulcer among 70,310 case histories of patients admitted to hospitals during pregnancy. However, it is possible that closer investigation of the nature of gastrointestinal complaints during gestation would reveal that such a lesion occurs more commonly than is ordinarily suspected.

Another observation made by Sandweiss and his associates[4] was that 46.7 per cent of 30 women with peptic ulcer showed pituitary, thyroid, or gonadal abnormalities. Bockus[2] states that the female patient with ulcer should be surveyed from the standpoint of endocrine abnormality because of the high incidence of endocrinopathies reported among women having peptic ulcer.

Experimental evidence further supports the theory that an endocrine factor is in some manner concerned in the control of gastric secretion. Sandweiss and his co-workers[3, 4] injected anterior pituitary-like hormone (chorionic gonadotropin) into laboratory animals following Mann-Williamson operation and noted a reduction of the incidence of jejunal ulcer. Furthermore, these investigators,[3, 4] as well as other workers,[5, 6] found that extracts of pregnancy urine or urine extracts from nonpregnant women without ulcer and from men similarly free from peptic ulcer caused a decrease in peptic ulcer in experimental animals. According to Gray[7] and Friedman and Sandweiss,[8] larger doses of such ulcer-preventive urine extracts also inhibit gastric secretion to some degree. Culmer, Atkinson, and Ivy[6] found that the injection of chorionic gonadotropin into dogs with Pavlov pouches greatly diminished the secretion

of free and total hydrochloric acid, even after histamine. They were unable to produce such an effect with any other hormone.

Reports by Nakai,[9] Arzt,[10] Mason,[11] and Anderson[12] indicate that early in pregnancy there is a marked diminution of free hydrochloric acid secretion. Arzt and Anderson also pointed out that the lowest secretion of free acid coincides with that period of pregnancy in which nausea and vomiting are common. Strauss and Castle[13] not only confirmed the presence of diminished gastric secretion in early pregnancy in normal women, but also showed that there is a rise in the secretion of free hydrochloric acid in the last month of pregnancy, and a still greater increase immediately or shortly after delivery. Way[14] has presented evidence to show that in human pregnancy there is an inversely proportional relationship between the free and total acid in the gastric secretion and the amount of chorionic gonadotropin in the urine. The normal peak of chorionic gonadotropin excretion in the urine which occurs within the first trimester of gestation, with a subsequent decline, is too well known to require discussion.

The inhibiting influence of extracts of the posterior lobe of the pituitary gland on gastric secretion was reported by Pol[15] and confirmed by Hess and Gundlach,[16] and Dodds and his co-workers,[17] and Metz.[18] Erosions of the stomach or duodenum following repeated or large injections into experimental animals of preparations of posterior pituitary extract have been found by Nedzel,[19] Dodds and Noble,[17] Berg,[20] and Metz.[18] Nedzel considered these lesions to be the result of local ischemia due to intense vasoconstriction.

The following case report emphasizes the necessity for attaching greater importance to gastrointestinal symptoms occurring during the latter months of pregnancy:

K. C., a 35-year-old gravid white woman, was admitted April 8, 1946, to Frankford Hospital on the obstetric service, complaining of heartburn, sour belching, and vomiting blood. She menstruated last on July 27, 1945. The expected date of delivery was May 2, 1946. About March 18, 1946, the patient began to experience epigastric discomfort one to one and one-half hours after taking food or medication. At this time heartburn and sour belching were also noted. However, although only casual mention of them was made on her visit to her physician on March 25, these symptoms increased in intensity so that by April 1 the upper abdominal discomfort had reached such proportions as to cause the patient to eat very little. There had also appeared pain in the back coincident with and at a point opposite the epigastric pain. The patient also began to vomit spontaneously, which afforded her relief from her symptoms. The stools had been black for several months because of ferrous sulfate which had been prescribed because of a mild anemia of pregnancy. Having stopped all medication for one week on her own initiative because of the severe epigastric pain, the patient became alarmed when she saw that the stools continued to be tarry. On April 7 she noted blood in the vomitus and on April 8, during a routine office visit, acquainted her physician with the severity of her complaints for the first time.

The patient's past medical history included mumps and measles in childhood and pleurisy at the age of 28 years. The systemic review was negative except for the gastrointestinal tract. In 1930, as a student nurse, the patient began to experience repeated attacks of acute epigastric pain. In 1931, following appendectomy for this complaint, she was free from discomfort for several months. However, the symptoms reappeared, remaining without interruption for several weeks at a time. The patient could not recall any relationship to food or to any procedure or medication taken for relief of the pain. There was no associated heartburn, sour belching, vomiting, or melena. Ques-

tionable jaundice appeared on one occasion. In 1938, following cholecystectomy, she again experienced a temporary remission of symptoms. The pathologist reported that the gall bladder showed chronic cholecystitis and cholelithiasis. Thereafter, at intervals of three to six months recurrences of epigastric pain were relieved by nonsurgical biliary drainage. Fractional gastric analysis, which was done during the course of this series of biliary drainages, was said to be normal. Radiographic studies were not made. The patient became free from gastrointestinal symptoms about October, 1942, and remained so until the last trimester of the present pregnancy.

As a child the patient had been thin, but became rather obese at puberty, retaining this tendency to the present time. Menstruation began at the age of 13 years, was regularly established from its inception at a 28-day interval, with a normal flow lasting four to five days. She was married in 1944 at the age of 34 years. In 1945, the basal metabolic rate was minus 8 per cent. In April, 1945, the patient aborted spontaneously after six weeks of pregnancy. For this reason she was maintained on oral progestin during the course of the present pregnancy. The family history contains no relevant data.

When seen by me on April 11, 1946, sixty hours after her admission to the hospital, the patient had shown some improvement in that the vomiting had largely, although not completely, subsided, there had been no hematemesis for forty-eight hours, and the pain had abated somewhat. Physical examination revealed an obese, slightly pale, gravid woman with no definite endocrine or other abnormalities. The blood pressure was 120/80. At this time the blood count showed hemoglobin 12 Gm. (81 per cent); erythrocytes, 3,700,000; and leucocytes, 14,900. Urinalysis was negative except for the presence of a trace of albumin.

The patient was placed on a Meulengracht regime, together with phosphalgel, tincture of belladonna, and phenobarbital. During the night of April 12 she suffered a severe gastrointestinal hemorrhage, as evidenced by the rapid appearance of marked pallor, weakness, dyspnea, and apathy. Early on April 13 the blood count revealed hemoglobin 3.5 Gm. (24 per cent); erythrocytes, 2,050,000; and leucocytes, 11,000. Repeated small transfusions of whole blood failed to halt the downward course of the blood count which, on April 16, reached a level of 2.7 Gm. (19 per cent) hemoglobin, 1,550,000 erythrocytes, and 27,000 leucocytes (neutrophiles 84 per cent, lymphocytes 9 per cent, monocytes 7 per cent). Surgical intervention to halt the gastrointestinal hemorrhage was considered out of the question. Cesarean section was believed equally hazardous. Later in the day (April 16) neither fetal heart sounds nor movement could be detected. On April 17 it was noted that the patient's digestive complaints had abated very markedly. From that point the manifestations of peptic ulcer continued to improve progressively, and there was good response to transfusions and no further sign of hemorrhage.

A stillborn, somewhat premature male child was born spontaneously on April 19. The mother showed no ill effects from six hours of labor. The puerperium was uneventful.

On May 2, fractional gastric analysis revealed the results shown in Table I.

Radiographic study on May 3 was reported as showing the esophagus and stomach to be normal in all respects. "The pylorus opened immediately. The duodenal cap was readily visualized and was seen to be large and rather flabby in tone. At the base, near the lesser curvature side of the cap, was a persistent small filling defect with a small fleck of barium in its center. The stomach was completely empty within three hours after the ingestion of the opaque meal."

TABLE I

TIME	TOTAL ACIDITY	FREE ACIDITY	OCCULT BLOOD
Fasting	43	23	very faint trace
15 min.	30	10	very faint trace
30 min.	35	25	negative
45 min.	70	28	negative
1 hour	80	40	negative
75 min.	90	40	very faint trace
90 min.	75	30	positive

When the patient was discharged on May 24, 1946, her blood count showed hemoglobin 10 Gm. (68 per cent), erythrocytes 4,170,000, and leucocytes 7,300. Her digestive symptoms had almost completely disappeared and, except for very occasional mild epigastric distress, she has remained free from gastrointestinal complaints.

Comment

The impression that pregnancy causes beneficial effects in the course of peptic ulcer has some experimental and clinical basis to support it. However, it appears that such favorable influences can be expected only in the early months of gestation. In the last trimester, and particularly shortly after delivery, endocrine influences may cause ulcer complications of a serious, and even fatal, character. It becomes necessary, therefore, to give more than casual attention to complaints referable to the upper gastrointestinal tract during pregnancy. A history suggestive of previous gastroduodenal ulcer should raise the possibility of reactivation of the lesion during the course of the gestation. Sandweiss[1] has emphasized the fact that most peptic ulcer patients have a "past." As in the present case, the routine administration of iron may mask tarry stools due to gastroduodenal bleeding. More frequent blood counts and even examination of the stool for occult blood, after suitable preparation of the patient, may give important information in women less seriously affected than the case reported.

Failure to observe the indications of possible peptic ulcer may result in serious consequences not only for the mother but for the fetus as well. Sandweiss[1] noted that in the 14 cases of maternal deaths reviewed by him, perforation of or hemorrhage from peptic ulcer occurred immediately or shortly after birth of a premature or a full-term child. In the present case, it seems likely that the profound anemia in the mother resulted in anoxia which was the immediate cause of fetal death. It is probable that the dramatic change in the patient's course, which followed immediately after death of the fetus, occurred as a result of the sudden alteration in endocrine influences.

References

1. Sandweiss, D. J., Podolsky, H. M., Saltzstein, H. C., and Farbman, A. A.: AM. J. OBST. & GYNEC. **45**: 131, 1943.
2. Bockus, H. L.: Gastroenterology, ed. 2, Philadelphia, 1946, W. B. Saunders Co., Vol. 1, p. 340.
3. Sandweiss, D. J., Saltzstein, H. C., and Farbman, A. A.: Am. J. Digest. Dis. **5**: 24, 1938.
4. Sandweiss, D. J., Saltzstein, H. C., and Farbman, A. A.: Am. J. Digest. Dis. **6**: 6, 1939.
5. Gray, J. S., Wieczorowski, E., and Ivy, A. C.: Science **89**: 489, 1939.
6. Culmer, C. V., Atkinson, A. J., and Ivy, A. C.: Endocrinology **24**: 631, 1939.
7. Gray, J. S.: Am. J. Digest. Dis. **8**: 365, 1941.
8. Friedman, M. H. F., and Sandweiss, D. J.: Am. J. Digest. Dis. **8**: 366, 1941.
9. Nakai, T.: J. Biochem. (Tokio) **5**: 465, 1925.

10. Arzt, F.: Am. J. Obst. & Gynec. **20**: 382, 1930.
11. Mason, L. W.: Colorado Med. **28**: 392, 1931.
12. Anderson, D. F.: J. Obst. & Gynaec. Brit. Emp. **39**: 558, 1932.
13. Strauss, M. B., and Castle, W. B.: Am. J. M. Sc. **184**: 655, 1932.
14. Way, S.: Brit. M. J. **2**: 182, 1945.
15. Pol, J.: Deutsche Med. Wchnschr. **42**: 1030, 1916.
16. Hess, W. R., and Gundlach, R.: Arch. f. d. ges. Physiol. **185**: 137, 1920.
17. a. Dodds, E. C., and Noble, R. L.: Proc. Roy. Soc. Lond., S. B. **30**: 815, 1935.
    b. Dodds, E. C., Noble, R. L., Scorff, R. W., and Williams, P. C.: Proc. Roy. Soc. Lond., S.B. **123**: 22, 1937.
18. Metz, M. H.: Texas State J. Med. **34**: 295, 1938.
19. Nedzel, A. J.: Arch. Path. **26**: 988, 1938.
20. Berg, M.: Am. J. Digest. Dis. **7**: 78, 1940.

MONOAMNIOTIC TWINS

DONALD COULTON, M.D., ARTHUR T. HERTIG, M.D., AND W. NEWTON LONG, M.D.
BOSTON, MASS.

(From the Departments of Pathology and Obstetrics, Harvard Medical School and the Boston Lying-in Hospital)

MONOAMNIOTIC twins are of interest because of their extreme rarity and the high incidence of fetal death associated with this placental anomaly. In 1935, Quigley[1] collected 109 cases from the world's literature, in only 17 of which both infants survived, although in 20 other cases one infant survived. This author added one new case in which one twin survived, this being the first case in American literature that had not ended fatally for both infants.

Since 1935, five more cases have appeared in the English literature; four American, and one British.[2-6] Of these, two resulted in twin live-births,[4, 5] although one twin of the first set died thirty hours after delivery. In the remaining three sets of twins there was one live baby and one anencephalic monster. (See Table I.)

TABLE I.

YEAR	AUTHOR	NUMBER OF CASES	DOUBLE LIVE-BIRTHS	SINGLE LIVE-BIRTHS	MONSTROSITIES
1700-1935	Quigley	109	17	20	8
1935	Rucker	1		1	
1935	Litt and Strauss	1			1
1936	Frewer	1	1		
1940	Parks and Epstein	1	1		
1942	Jones	1			
1945	Coulton, Hertig and Long	2	2		
	Total	116	21	21	9
	Per cent		18.9	18.9	7.8

According to Quigley, who discusses the possible mechanisms of development of monoamniotic twins, monstrosities occur frequently, eight having been encountered in his series of 109. One is described in the five subsequent cases. The high fetal mortality, however, is due chiefly to tangling and knotting of the cords around each other and around the infants. True knots of the cords occurred in all of the five cases reported since 1935, even in the sets of living twins. Thus knotting of the two cords, usually causing fetal death of one or both infants, seems to be the common accompaniment of twins not separated by a membranous partition.

Recent observation of early embryos by one of us (A. T. H.) allows estimation of the time at which the fertilized ovum must have split to form two normal embryos within a single amnion. This estimation is arrived at as follows: The inductive force in the formation of the amnion is the presence of the embryo.[7] Had the germ disc split before the formation of the amnion, presumably two amnions would then have formed in response to the presence of the two embryos. Therefore, at the time of amnion formation the split had not yet

occurred. Since the amnion forms during the seventh to the thirteenth day following fertilization,[7] the split could not have occurred before the seventh day. On the other hand, when the split occurred, the cells of the germ disc were sufficiently undifferentiated to form two equally potential halves. This is only possible before the germ disc shows a single axial arrangement, at which time the primitive streak simultaneously appears. These are first seen in the 13½-day-old embryo.[8] We can be reasonably sure, therefore, that the split forming normal monoamniotic twins occurred sometime after the seventh and before the thirteenth days. Splitting of the germ disc before the seventh day should reasonably produce diamniotic twins, and after the thirteenth day, monoamniotic Siamese twins and monstrosities.

Two cases are here described, one from the Richardson House of the Boston Lying-in Hospital and the other from the ward service of the latter institution. They are of interest because there was no tangling or knotting of the cords, either together or singly, and as would be expected, both pairs of infants were born alive and survived, despite being monoamniotic. These are the third and fourth cases in American literature of double live-births; the second and third cases of double infant survival and the first two cases without tangling or knotting of the cords.

CASE 1.—The patient was a white, married, gravida i, due Oct. 1, 1945. She was admitted on September 18 because of spontaneous rupture of the membranes, not in labor.

Family History.—There were no twins in the patient's family. The patient's husband was a twin, his mother having borne two sets of twins.

Menarche occurred at the age of 14-15 years, periods occurring every twenty-eight days, lasting five days, with moderate amounts of flow and no pain. Her last menses began Dec. 24, 1944.

Prenatal Course.—May 25, 1945: General physical examination was essentially negative. Pelvic measurements indicated a gynecoid pelvis. The introitus was nulliparous. Inspection of the cervix was unremarkable except for a small amount of white discharge. The uterus was enlarged to the size of a five months' pregnancy. It was thought that the presenting part was not the head.

August 9: The uterus seemed slightly larger than average for the duration of gestation. A head was felt in the fundus and a breech by vaginal examination. External version was done without difficulty, after which a head was felt dipping into the pelvic brim. A fetal heart could be heard below and also above the umbilicus following the version. X-ray examination revealed a gynecoid pelvis with prominent coccyx and a twin pregnancy.

September 5: By rectal examination, a head was felt to be engaged and the cervix nearly taken up.

Laboratory studies were negative throughout. Her blood was Group AB Rh positive.

Labor.—Early in the morning on September 18, the patient reported that the membranes had ruptured with the painless escape of fluid from the vagina. She was admitted to the Richardson House at 4:45 A.M. with definite evidence of ruptured membranes, not in labor. The cervix was taken up and 2½ fingerbreadths dilated by rectal examination. She was given seconal and demerol sedation. At 7:25 A.M. active labor was in progress with strong, frequent contractions. Additional seconal and scopolamine sedation was given. At 7:45 A.M. the os was almost fully dilated. Full dilation was reached about

11:00 A.M. and, after more than an hour in the second stage of labor without progress, preparations were made for delivery.

Delivery.—Under spinal anesthesia, a head was felt in the midpelvis in left occipitoposterior position. Midforceps rotation and extraction were done with Kielland forceps aided by a median episiotomy. A long version glove was then put on, and the second baby delivered from right occipitoanterior by internal podalic version and breech extraction. The cord was once around the neck. No separate sac of membranes was encountered around the second baby. One ampule of pituitrin was given after the birth of the second baby. A single placenta, complete with membranes and two cords, was expressed after which one ampule of ergotrate was given intravenously.

Infants.—The first baby was a 5 pound, 11 ounce male born at 12:35 P.M. He was slightly cyanotic at first but breathed well. Mucus was removed from the upper respiratory passages and oxygen administered, after which his color was excellent. There were no abnormalities except phimosis.

The second baby was a 4 pound, 11 ounce male born at 12:44 P.M. He was moderately white at first but rapidly became pink, breathing and crying well. There were no abnormalities except phimosis.

Both babies were taken to the premature nursery and given continuous oxygen therapy.

Postpartum Course.—The patient's postpartum course was uneventful except for uterine subinvolution corrected by additional ergotrate and daily hot douches. She was unable to nurse, having insufficient milk. She was discharged on September 30, her twelfth postpartum day, taking the first baby with her. His discharge weight was 5 pounds, 6½ ounces, and his condition good.

The second baby was discharged in good condition on Oct. 7, nineteen days after delivery, weighing 5 pounds, 6 ounces.

Placenta.—Gross: The placenta weighed 820 Gm., and measured 26 by 27 by 2 cm. The membranes were ruptured from the placental margin. There was only one amniotic cavity, no membranous partition being present between the two umbilical cords. One cord was attached 4 cm. from the placental margin, and measured 41 cm. in length; the other cord also arose 4 cm. from the placental margin, 8 cm. from the first, and measured 39 cm. in length. The cords were not tangled or knotted at any point. The fetal vessels from the two cords anastomosed at several points over the fetal surface. The maternal and cut surfaces were unremarkable.

Microscopic: Two slides revealed the villi to be of the mature type. Subsyncytial fibrinoid degeneration and calcification were present in moderate amounts. The villous vessels were slightly dilated. There was physiologic intimal thickening of the chorionic vessels. The decidua was unremarkable.

CASE 2.—The patient was a 21-year-old Negro, married, gravida i, due March 8, 1946. She was admitted to the hospital on March 7, 1946, in desultory labor because of spontaneous rupture of membranes.

There were twins in the patient's family, two sets having occurred in the previous generation.

Past History.—As a result of a fall at the age of three the patient had scoliosis, for which she underwent a bone fusion operation in 1938. Her only other serious illnesses were pneumonia in 1937 and several bouts of pyelonephritis treated at another local hospital, most recently in 1944.

Menarche occurred at the age of 13 years. Periods have always been irregular, occurring every twenty-one to thirty-five days, lasting four days. Her last menses began June 1, 1945.

Prenatal Course.—Early in pregnancy the patient was admitted to another hospital complaining of nausea and vomiting and costovertebral-angle pain. Urological studies revealed slight impairment of renal function, but because of the coexisting pregnancy, it was decided that most of her symptoms were due to hyperemesis gravidarum.

On her first prenatal visit to this hospital the significant findings were a contraction of the pelvic inlet, a uterus enlarged out of all proportion to the dates, and a moderate anemia. A roentgenogram obtained at this time confirmed the diagnosis of twins and of asymmetry of the pelvis.

Urological studies confirmed the presence of moderate hydronephrosis and hydroureter. Gestation was otherwise uncomplicated.

Labor.—The patient was admitted to the hospital as noted five hours after the onset of labor and three hours after rupture of the membranes. The first fetus was presenting by vertex which was well engaged, and the cervix partly dilated. Following a hot enema, labor became satisfactory in effacing and dilating the cervix. After fourteen hours of labor with seconal, scopolamine, apomorphine analgesia, she was delivered by forceps extraction of a 5 pound, 5 ounce female infant in good condition. Spinal anesthesia was employed. Meanwhile the arms of the second fetus had prolapsed into the vagina. These were replaced, and delivery carried out by internal podalic version, breech extraction, with forceps to the aftercoming head. The second infant, also female, weighed 5 pounds, 14 ounces. She did not cry for three minutes, but her color became good after the nasopharynx was aspirated. The placenta separated in six minutes and was delivered by simple expression. The patient withstood the procedure well, having lost an estimated 200 c.c. of blood. The right mediolateral episiotomy was repaired.

Postpartum Course.—The only complication of the puerperium was cracking of the nipples, necessitating the substitution of formula beginning on the sixth postpartum day. The lesions were treated with penicillin ointment, ice bag, and binder. The mother and both babies were discharged on the sixteenth postpartum day, the first baby having gained one-half ounce and the second having lost three ounces.

Placenta.—The placenta weighed 1,080 Gm. and measured 21 by 21 by 2.5 cm. The cord of the first twin (marked at delivery) was inserted eccentrically and measured 66 cm. in length. No knots or tangles were noted in the cords at any point. The fetal surface of the placenta was homogeneously slate-blue in color with two small white indurated areas suggestive of subchorionic fibrin deposition. No amniotic partition could be discovered. The fetal vessels showed marked interdigitation with actual anastomosis. Membranes were ruptured far from the placental margin. Lobulations upon the maternal surface were normal in depth. There was a moderate degree of calcification in the decidua. The cut surface was purple in color, moist, and granular in texture.

Summary

1. A brief review of the literature on monoamniotic twins is given.

2. An estimation of the time at which the germ disc split to form monoamniotic normal twins is made.

3. Two new cases of monoamniotic twins are described in which both sets of twins lived, this being the second and third instances in American literature of double survival.

References

1. Quigley, James K.: Am. J. Obst. & Gynec. **29**: 354-360, 1935.
2. Rucker, M. P.: Am. J. Surg. **28**: 175, 1935.
3. Litt, S., and Strauss, H.: Am. J. Obst. & Gynec. **30**: 728-730, 1935.
4. Frewer, Edward: Brit. M. J. **1**: 159, 1936.
5. Parks, John, and Epstein, J. R.: Am. J. Obst. & Gynec. **39**: 140-142, 1940.
6. Jones, Warren E.: Am. J. Obst. & Gynec. **43**: 130-132, 1942.
7. Hertig, Arthur T.: Yale J. Biol. & Med. **18**: 107, 1945.
8. Heuser, H., Rock, J., and Hertig, A. T.: Contrib. to Embryol. **31**: No. 201.

THE SIGNIFICANCE OF DECIDUAL POLYPS IN OTHERWISE NORMAL PREGNANCIES

R. L. Haas, M.D., Ann Arbor, Mich.

(From the Department of Obstetrics and Gynecology, University of Michigan Hospital)

ONE of the occasionally perplexing problems confronting the obstetrician and gynecologist is the management of abortions. The decision as to whether a threatened abortion has become inevitable is sometimes difficult to make. The passage of tissues from the uterus is commonly assumed to mean that continuation of the pregnancy is no longer possible,[1] and often this is a signal to empty the uterus by curettage.

It is the purpose of this paper to report three cases which emphasize the importance of determining the nature of any tissue passed. That the expulsion of tissue does not always signify inevitable loss of the pregnancy is revealed in the following case reports. In a little over one year three patients were seen during early pregnancy, all threatening to abort as indicated by uterine bleeding and the passage of tissue. However, the tissue proved to be decidua, and all three pregnancies progressed to term with delivery of normal infants.

Investigation of the literature, including popular textbooks on obstetrics, fails to reveal any reference to such a course of events in early pregnancy, although there is described[2] a diffuse decidual hyperplasia, noninfectious in origin, which may lead to late antepartum bleeding, and thus be confused with placenta previa.

Case Reports

Case 1.—O. T., No. 545059, para 0, gravida i, first seen on April 3, 1944. The patient stated that her last menstrual period had occurred Jan. 11, 1944. Early in February there had been slight vaginal bleeding. There were no associated cramps or pain. Examination showed the usual changes, of early pregnancy, with no palpable adnexal pathology suggestive of an ectopic. However, there were two small cervical polyps which did not bleed on sponging, and, in addition, a small bit of white material in the external cervical os which proved to be the lower end of a strip of tissue two inches in length and one-eighth of an inch in diameter, resembling a fetal umbilical cord. A diagnosis of probable incomplete abortion was made, and the patient was admitted for observation and possible curettage. Microscopic examination of the strip of tissue showed it to be decidua with some necrosis and purulent inflammation. The Aschheim-Zondek test gave a normal positive reaction. In the light of these findings curettage did not seem justified, and, after three days, the patient was discharged from the hospital. The remainder of her pregnancy was uneventful and culminated in delivery of a 6 pound, 10 ounce normal female infant, after a nineteen-hour labor. The third stage of labor was normal and the placenta revealed no pathology.

Case 2.—I. Mc., No. 445063, para i, gravida ii, first seen on Aug. 17, 1944, the last menstrual period having occurred on May 4, 1944. On July 17, after driving a tractor for two hours, she noted a bloody brown discharge associated with mild suprapubic soreness, but no other symptoms. The discharge continued daily—more profuse with activity—for one month, when she first sought medical

attention. Upon examination the uterus was found to be compatible with a 3½- to 4-month pregnancy (perhaps a little larger than the menstrual history would indicate, thus suggesting the possibility of a mole). The adnexa were negative to palpation. The cervix was dilated 1 cm. by a polypoid mass of tissue which bled briskly upon sponging. This tissue was removed with a biopsy forceps. Microscopic study showed that the entire specimen consisted of decidua. There were inflammatory infiltrations upon the surface. During the second trimester there were frequent episodes of slight bleeding and cramping, but the last trimester was uncomplicated. The patient delivered an 8 pound, 7 ounce infant at term after a sixteen-hour labor. The third stage was normal. The placenta revealed a succenturiate lobe, but no other abnormality.

CASE 3.—M. T., No. 571771, para 0, gravida i, first seen on June 22, 1945. Her last menstrual period had occurred on May 29, but was five days late. After five days (her usual duration) the flow stopped, but two days later it recurred and was profuse. She also had marked nausea at this time. The bleeding ceased following the taking of some tablets, given by another physician. However, it recurred intermittently until she was first examined by me on June 22, 1945. Examination revealed the uterus to be soft and slightly enlarged, and there were a few small bits of necrotic appearing tissue in the external os. These were removed and proved to be decidua, largely necrotic, and with leucocytic infiltrations. No chorionic villi were found. The Aschheim-Zondek test was positive in 1:50 dilution, but a few days later gave only a normal positive reaction. For the next month the patient continued having daily a slight brown or pink discharge. Thereafter, the pregnancy progressed normally, and a 5 pound, 15⅔ ounce male infant was born at term after a one hour and forty minute labor. The third stage and placenta were normal.

Discussion

It is interesting to speculate as to the origin of the decidual tissue passed by these patients. Possible explanations are:

1. The development of the decida may have been unusually exuberant resulting in a condition similar to the diffuse decidual hyperplasia of earlier writers,[2] with protrusion of some of the tissue through the cervical canal.

2. Ectopic decidua may be found in the cervical canal (where it rarely occurs, according to Taussig[3]) with extrusion of a portion of it. In view of the absence of bleeding in the latter part of pregnancy the first theory would seem untenable, for such bleeding is characteristic of diffuse decidual hyperplasia. Furthermore, Stander[4] has suggested that such a pathologic decidua may interfere with placental separation, which was not encountered in these patients.

The second possibility—ectopic decidua—appears more plausible. No interference with the course of pregnancy or labor would be expected in such a condition.

The passage of decidua in early pregnancy is frequently assumed to indicate the presence of an ectopic pregnancy. That this was not the case in the three patients cited was borne out by the absence of palpable adnexal pathology, and by their subsequent course. This point is of considerable interest and importance, because not infrequently the differentiation between a threatened abortion and an ectopic pregnancy must be made. Passage of decidua would appear to bolster the latter diagnosis (and indeed it often does) but not invariably, as proved by the cases cited here.

As an aid in ruling out the diagnosis of abortion in these cases, use was made of the Aschheim-Zondek test. This test was positive in all three instances. In incomplete or complete abortion one would be more likely to obtain a negative, or incompletely positive reaction.

The practical significance, therefore, of these cases is that the true nature of any tissue passed by a patient threatening to abort must be determined by microscopic study. If fetal elements are included, then one must assume that the abortion is inevitable. If only decidua is found, ectopic pregnancy must be considered. If this can be ruled out, then one is probably dealing with an otherwise normal pregnancy which will require no special care. A positive pregnancy test further confirms this assumption.

References

1. Taussig, F. J.: Abortion, Induced and Spontaneous, St. Louis, 1936, The C. V. Mosby Co., p. 143.
2. Riotte, A. E.: Gynec. et. Obst., **9**: 23-49, 1924.
3. Taussig, F. J.: Abortion, Induced and Spontaneous, St. Louis, 1936, The C. V. Mosby Co., p. 133.
4. Stander, H. J.: Williams Obstetrics, New York, 1941, D. Appleton-Century Company, p. 721.

ENDOMETRIAL CYST IN AN EPISIOTOMY SCAR

JOHN C. BROUGHER, M.D., F.A.C.S., VANCOUVER, WASH.
(From the Vancouver Clinic)

ABERRANT endometrial tissue has been found and reported in numerous locations. The chief extrauterine sites in which endometrial development may occur, according to Novak,[1] are the following: (1) ovaries, (2) uterine ligaments, (3) rectovaginal septum, (4) the pelvic peritoneum, covering the uterus, tubes, rectum, sigmoid, and bladder, (5) umbilicus, (6) laparotomy scars, (7) hernial sac, (8) appendix, (9) vagina, (10) vulva, (11) cervix, (12) tubal stumps. There may also be involvement of the brachial region, the thighs, and even the lungs.

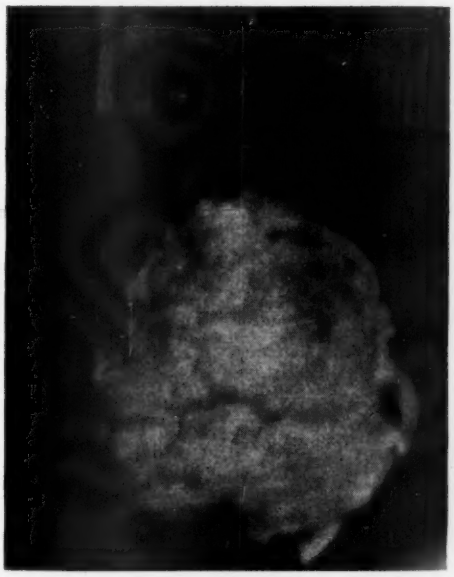


Fig. 1.—Endometrial cyst removed from episiotomy scars. Gross tumor measured two centimeters in diameter.

Case Report

Mrs. H. A. S., aged 38 years, housewife; good general health; two children, ages 4 and 2 years. Menstrual cycle regular and normal. When the last child was delivered, an episiotomy was performed. About a year after birth of the last child the patient noticed a nodule or swelling located at the site of the left mediolateral episiotomy scar. This gradually became larger as time advanced, and became greatly distended and painful during menstruation. It exhibited a bluish discoloration at this time. On March 21, 1946, an office examination revealed this growth to be about two and one-half centimeters in diameter and rather soft and cystic in appearance. It was opened, and dark-colored blood and what appeared to be disintegrated mucosa drained.

At this time a tentative diagnosis of endometrial cyst was made. On April 10, 1946, the patient entered the hospital and an operation was performed for removal of the cyst.

The following pathologic report was recorded:

Gross Examination.—The cyst measured two centimeters in diameter and was removed from the left side of the vulva. The cystic walls were removed in their entirety. A portion of the inner coat was lined with a soft velvety-like mucosa that had a brown yellowish color. Some of this inner coat penetrated the entire thickness of the walls (Fig. 1).

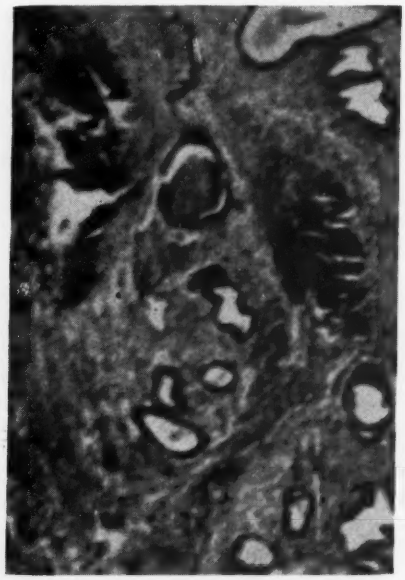


Fig. 2.—Microscopic appearance of endometrial transplantation of episiotomy scar. The well-formed endometrial glands are lined with a single layer of tall cells. The stromal cells are fairly well defined.

Microscopic Examination.—In this tissue there was a great variation of the histologic picture. In some areas there was a decided resemblance of the uterine mucosa, while in other regions this condition did not prevail. The well-formed glands were lined with a single layer of tall cells, and in places the stromal cells were well defined. In other places there was considerable disintegration of the mucosa with discoloration, the result of an old hemorrhage. In some regions there were islands of small poorly formed follicles which were surrounded by numerous stromal cells. Again, there were areas of hemorrhage only. In places this mucosa was invading the other walls of the cyst (Fig. 2).

I wish to thank Dr. M. Holmes of St. Joseph's Hospital, Vancouver, Washington, for photographing and describing the tissue reported in this paper.

Reference

1. Novak, Emil: Gynecologic and Obstetrical Pathology, ed. 2, Baltimore, 1944, Williams & Wilkins.

FULL-TERM LABOR AFTER A SUBTOTAL HYSTERECTOMY IN A DOUBLE UTERUS

H. Acosta-Sison, M.D., Manila, P. I.

(From the Department of Obstetrics, University of the Philippines)

THE title above sounds apocryphal, but it is nonetheless literally true. On Oct. 2, 1944, because of impending uterine rupture and exposure to infection, the author performed a Porro cesarean section in a woman who, on Sept. 12, 1946, delivered spontaneously her third full-term baby after one-half hour of second stage labor pains. She and her child were discharged from the hospital on Sept. 21, 1946. The full history of the case is as follows:

A. D., para iii, aged 25 years, was admitted to Philippine General Hospital for labor pains. The baby was full term in left occipitoanterior position with the head engaged. After one-half hour of second stage pains, she delivered spontaneously a healthy infant without analgesia or anesthesia.

Previous Pregnancies.—The first pregnancy was associated with marginal placenta previa ending in spontaneous delivery of a small baby less than 6 pounds after a prolonged labor of three days and with the help of pitocin. This child is now 4 years old.

On Oct. 2, 1944, she was admitted to the Philippine General Hospital in serious condition because of dystocic full-term labor of her second pregnancy. She was under the care of an outside private physician who gave her 1 ampule of pituitrin after she had suffered nine hours of strong labor pains and had not succeeded in making the head engage. On admission to the hospital, her temperature was 37.2° C., pulse 103, respiration 20. The uterine enlargement which took an oblique direction with the fundus toward the epigastrium was divided by a transverse groove situated a little above midway between the umbilicus and symphysis. The upper uterine segment was in tetanic contraction, and the lower segment was markedly bulging and tender. The head was the presenting part and was not engaged. No fetal heart was audible. Vaginal examination showed the cervix to be completely dilated, the membranes ruptured, a prolapsed nonpulsating cord, and a high nonengaged head. Pushing the right and posterior fornices toward the vaginal cavity was a tumor mass the size of a large apple which obstructed the engagement of the head.

The diagnosis of impending, if not actual, uterine rupture was made, and laparotomy under local anesthesia was immediately performed. On opening the peritoneal cavity free blood was encountered, but no complete uterine rupture was found. The lower uterine segment along with the bladder was markedly bulging and thinned out. Since many vaginal examinations outside and inside the hospital had been performed, a Porro cesarean section was thought to be the operation indicated. Accordingly, after extracting a large dead child together with its already separated placenta through a longitudinal incision at the upper segment, a supravaginal hysterectomy was made. The uterus was separated from the left broad ligament in the usual manner. On the right side, however, the uterus was found to have neither tube nor ovary, nor was it connected with the right broad ligament. After putting a cervical drain and peritonizing the cervical stump, an examination of the pelvic cavity for the identification of the obstructing tumor showed another uterus enlarged to the size of two months' pregnancy, and to it was attached the right broad

ligament with its tube and ovary. It had its own lower segment connected with the cervix and vagina below. It was the mass in the pelvic cavity which blocked the passage of the fetus. The abdomen was closed after putting in a cigarette drain.

Aside from the purulent discharge through the drainage wound and a low-grade fever for eight days, the postoperative course was satisfactory, considering the patient's condition before the operation. The abdominal wound finally healed by first intention.

On Oct. 26, 1944, or twenty-four days after the operation, the introduction of the uterine sound through the cervical canal showed a uterine cavity of 8 centimeters. Toward the left side, the sound could reach only as far as 4 cm., showing the depth of the cervical stump of the hysterectomized uterus.

Comments

Obstetric literature including the current textbooks would call the above developmental anomaly as *uterus bicornis unicollis.* I had proposed for it the term *uterus lidelphys unicollis.* Textbooks heretofore have assigned the term uterus didelphys to two separate uteri with their corresponding cervices. To this form of anomaly I proposed the name *uterus didelphys bicollis.*

The term uterus bicornis unicollis should be limited to those cases where the separation of the uteri is at the upper segment, not in the region of the internal os which is the condition of the present case. The first report of a case of uterus bicornis unicollis in the Philippines was made by me in 1938.[2] It was discovered on laparotomy performed for what was supposed to be unruptured tubal pregnancy. What was found was pregnancy of one horn of a uterus bicornis unicollis. The separation of the two uteri was at the upper segment. This patient had given normal spontaneous births without difficulty to ten full-term babies.

In cases of bicornis unicollis (in its limited application proposed by me) because the separation of the uteri is at the upper segment, as long as both uteri have access to the vaginal canal, no dystocia is expected for when one horn becomes impregnated and rises above the pelvic cavity, it invariably raises its partner with it above the pelvic brim; whereas in cases of uterus didelphys unicollis (the new term proposed) as found in the patient here reported because the separation of the uteri is at the internal os or below it, when one uterus becomes impregnated, in its growth, it does not carry with it its fellow partner above the pelvic brim. On the contrary, the nonpregnant uterus because of its softened lower segment remains below the pelvic brim and because it also undergoes hypertrophy, as found in this case, it constitutes a dangerous obstacle to vaginal delivery of a full-term fetus. So that hysterectomy of the pregnant uterus in this case is more than justified. At the time of the operation, the indication was the prevention of the spread of infection. But, in retrospect, its performance removed the danger of causing an obstacle in the vaginal delivery of subsequent full-term pregnancies in this patient.

Braze[3] described a uterus similar to the one here reported. No obstructive labor occurred in his case because both uteri became pregnant at the same time ending in the spontaneous delivery of twins. However, three months after the delivery of the babies severe abdominal symptoms occurred in the patient that obliged Braze to laparotomize. He found one uterus was prolapsed and incarcerated. It is unfortunate that both uteri were extirpated.

Summary and Conclusions

1. Uterus didelphys unicollis is the term that should be applied to that developmental anomaly where there is complete external separation of the

uteri down to the level of the internal os but have one common cervix. This anomaly at full term will give rise to obstructive dystocia if one uterus becomes pregnant, for the nonpregnant uterus which also undergoes hypertrophy remains in the pelvic cavity.

2. Uterus bicornis unicollic should be applied to those cases where the external separation of the uteri is at the body or upper segment of the uterus. This anomaly does not give rise to dystocia as long as both uterine cavities communicate with the cervical cavity and vaginal canal. When one cornu becomes impregnated, it invariably lifts with it its fellow partner above the pelvic inlet.

3. There is no necessity of removing both uteri in uterus didelphys unicollis or uterus didelphys bicollis. One should be left in situ to perform its normal function.

The outcome of the case here reported justifies such a policy.

References

1. Stander, H. J.: Text Book of Obstetrics, New York, 1945, D. Appleton-Century Co.
2. Acosta-Sison, H., and Katigbak, J. R.: J. Philippine Islands M. A. **18**: 751, 1938.
3. Braze, A.: J. A. M. A. **123**: 474, 1943.

SIMULTANEOUS INTRAUTERINE AND EXTRAUTERINE PREGNANCY

CUTHBERT POWELL, M.D., F.A.C.S., AND ROBERT H. GOTTSCHALK, M.D.,
DENVER, COLO.

(From the Department of Obstetrics and Gynecology, University of Colorado School of Medicine)

THE first reported case of simultaneous intrauterine and extrauterine pregnancy was by Duverney[1] in 1708. The diagnosis was made at autopsy, death having occurred as a result of rupture of the pregnant tube in the third month of pregnancy.

In 1940, Mitra[2] extensively reviewed the literature on the subject. He stated that at that time not more than 304 cases had been recorded in the world literature, including German, French, and Russian. He added two cases of his own, bringing the total to 306. Although Stander[3] states that the condition occurs quite frequently and has been investigated by numerous writers, most observers consider the condition quite rare. Studdiford and Speck,[4] in 1944, reported 368 cases with 12 new instances. If one considers that only about 400 cases have been reported since 1708, it is certainly a rarity. Unquestionably many cases are not recognized and others, though recognized, are not reported but it is far from even an occasional experience for the average obstetrician.

In the large majority of cases the symptoms of extrauterine pregnancy predominate. The coincident intrauterine pregnancy is rarely found before operation. Rupture of extrauterine pregnancy most commonly occurs in the first three months.

The treatment of extrauterine pregnancy is definitely surgical, whether the diagnosis is made before or after rupture. A preoperative diagnosis of coexisting intrauterine pregnancy should not in any manner alter the indications for surgical interference. The surgery should be limited to the treatment of the extrauterine pregnancy, and should be as expeditious as is consistent with safety to the patient. Frequently it is impossible to determine definitely a coexisting uterine pregnancy at the time of operation, as in all cases of extrauterine pregnancy the uterus is somewhat enlarged and softened. The removal of such a uterus is definitely contraindicated.

Our report is that of a 25-year-old primipara having a simultaneous intrauterine and extrauterine pregnancy—operated upon following rupture, the intrauterine pregnancy continuing to term.

This patient entered the Colorado General Hospital on Feb. 5, 1945, with a complaint of pelvic pain for the past month. The pelvic pain occurred quite suddenly and became progressively worse until five days prior to hospital admission. At that time the patient experienced a sudden more severe pain confined to the left lower quadrant. This episode was accompanied by nausea and vomiting. The pain subsided in twenty-four to thirty-six hours. No

specific medication was taken. On the evening prior to hospital admission another episode of left lower quadrant pain occurred. The only therapy the patient had been receiving was some "endocrine injections" from her local doctor for her menstrual irregularities.

Menstrual periods had been of four to five days' duration and occurred every twenty-six to forty-five days. Patient's last normal menstrual period occurred between Oct. 24 and 28, 1944. During November and December the patient flowed one day at approximately the usual time. No vaginal bleeding had occurred since the last part of December, 1944.

Physical examination on admission revealed a white woman of stated age in only slight distress. Temperature was 99.8° F., pulse 120, and blood pressure 120/74. Physical examination was not remarkable except for tenderness on abdominal examination in both lower quadrants. There was some rebound tenderness, more marked on the left side. Pelvic examination revealed the cervix displaced to the right and softer in consistency than normal. A large tender fixed mass was palpable in the posterior cul-de-sac. The fundus of the uterus was not definitely palpable because of the thickness of the abdominal wall and rigidity.

Laboratory findings revealed hemoglobin 11 Gm., red blood cells 3,380,000, white blood cells 10,000, differential; 87 per cent polymorphonuclears, 11 per cent lymphocytes, 2 per cent endothelial cells. Urinalysis showed 3 plus pus cells, 2 plus acetone. Friedman's pregnancy test was negative. The preoperative diagnosis was pelvic abscess, and the possibility of a ruptured tubal pregnancy was considered. We were inclined to regard the menstrual history as unreliable in view of previous irregularity. On February 9, four days after admission, a posterior colpotomy was first done and old blood, blood clots, and fresh blood were encountered. A vaginal pack was inserted because of the amount of bleeding, and the patient was immediately prepared for a laparotomy. A suprapubic midline incision was made and a ruptured left tubal pregnancy was found. A fetus measuring 81 mm. in length, the left tube and ovary, which grossly contained a corpus luteum, and the products of conception were removed. About 250 c.c. of old and fresh blood were removed by aspiration. On inspection the right ovary also contained a corpus luteum. The uterus was about the size of a 2½ months' pregnancy and soft. A diagnosis of intrauterine pregnancy was made. A Penrose drain was placed through the vagina and 5 Gm. of sulfathiazole and sulfanilamide mixture were left in the pelvis. Postoperatively the patient was placed on 15 mg. of progesterone daily during her hospital stay and 5 mg. daily for fourteen days following her discharge. The Penrose drain was removed on the third postoperative day. The patient's convalescence was uneventful. She was discharged from the hospital on her fourteenth postoperative day.

The intrauterine pregnancy progressed satisfactorily, and a viable female child weighing 8 pounds, ½ ounce, was delivered with low forceps on Aug. 22, 1945. The child was normal except for a talipes equinovarus deformity of the right foot. Immediately post partum the uterus failed to contract satisfactorily and the patient lost approximately 500 c.c. of blood. Because of the blood loss, a whole blood transfusion was given. This case illustrates the importance of doing routine Rh blood grouping for transfusions in an obstetric ward, as this patient was Rh negative and her husband was Rh positive.

The negative Friedman test can perhaps be explained on the basis suggested by Buxton.[5] Pregnant patients who have been receiving estrogenic hormone frequently have a negative Friedman test. The secondary signs of pregnancy were minimal. The tender, hard mass present in the posterior cul-de-sac, temperature elevation, and evidence of pelvic pain of one month's duration thus are explained on a basis other than the development of a pelvic abscess which was our first impression.

References

1. Duverney: Oeuvres Anat., 1708, p. 355.
2. Mitra, Subodh: J. Obst. & Gynaec. Brit. Emp. 47: 206-212, 1940.
3. Stander, H. J.: Textbook of Obstetrics, New York, 1945, D. Appleton-Century Co., p. 777.
4. Studdiford, N. E., and Speck, G.: Am. J. Obst. & Gynec. 47: 118-121, 1944.
5. Buxton, R.: Virginia M. Monthly 71: 303-304, 1944.

GRANULOMA VENEREUM OF THE CERVIX

SWAN BURRUS, JR., M.D., GREENWOOD, MISS.
(From the Delta Medical Center)

GRANULOMATOUS lesions of the cervix have been described in the medical literature since 1928. Gardner, in that year, first suggested that such lesions might possibly be related to granuloma inguinale, yet it was not until 1937 that granuloma (inguinale) venereum of the cervix was established as an entity by Greenblatt and Pund when the pathognomonic cell was demonstrated in the cervical lesion.[1] Since that time 65 cases have been reported in the literature. In 1934 McGee reported eight cases of granuloma of the cervix diagnosed by biopsy. In none of these cases were the Donovan bodies demonstrated at the time. In 1939, Pund, Huie, and Gotcher, reviewing the Georgia Medical School files, discovered no cases prior to 1934 and nine cases from 1934 to 1938 from a total of 830 cervical biopsies. Arnell and Potekin reviewed all the cases of granuloma of the cervix at Charity Hospital from 1929 to 1937 and identified Donovan bodies in 17 cases (including four of McGee's cases in which the Donovan bodies were found). From 1937 to 1939, they demonstrated the specific histopathology of granuloma inguinale in 21 cases with granulomatous lesions of the cervix. From 1937 to 1939, as far as could be ascertained, seven additional cases were reported in the literature. In 1939, five instances of granuloma venereum of the cervix were reported by Henthorne.

There is a very definite racial difference in the incidence of the disease, the predilection for Negroes being far in excess of that for white individuals. In the Charity Hospital group, there were four cases in white females and 34 Negro cases. All of McGee's and the Georgia Medical School patients were Negroes.

Below are reports of two cases of granuloma venereum of the cervix which were treated at this center in July and September, 1946:

CASE 1.—A 26-year-old Negro single woman was admitted to the Delta Medical Center with a diagnosis of late latent syphilis. The patient had no gynecologic complaints and had had no pregnancies. Routine pelvic examination disclosed a small, 2 by 3 cm., cherry-red, velvety-soft, easily bleeding, irregularly outlined granulomatous lesion located on the anterior lip of the cervix. The lesion was well defined by a smooth, hypertrophied rolled edge. There were no vaginal lesions. Dark-field examinations were negative. Smears stained with Wright's stain revealed the typical intracytoplasmic Donovan bodies. The patient received tartar emetic twice weekly, under which treatment the cervical lesion healed rapidly. At the six-week check-up, the cervix appeared normal with no remaining evidence of the pre-existing lesion.

CASE 2.—A 20-year-old Negro woman was referred to the Delta Medical Center for treatment of "a luetic lesion of the cervix." The patient knew nothing of the lesion and gave no history of pain, discharge, or bleeding. There was one 18-month-old offspring and no history of other pregnancies. The patient had received 10 injections of an arsenical and three of bismuth for syphilis, three years ago. Vaginal examination revealed a 1 by 4 cm. irregular, dirty, friable, easily bleeding granulomatous lesion extending across the anterior lip of the cervix. Three smaller, separate, and distinct daughter lesions were

present on the anterior aspect of the vaginal vault adjacent to the cervical lesion. The lesions were quite odorous. Palpation disclosed that the lesions were soft and that the posterior vault was partially stenosed by firm cicatricial tissue. Dark-field examination of the lesions were negative. After repeated Wright-stained smears, the typical intracytoplasmic Donovan bodies were demonstrated. The patient received a ten-day course of penicillin, mapharsen, and bismuth for early latent syphilis, and then was started on gradually increased doses of tartar emetic. Daily examination during the course of antisyphilis therapy revealed no change in the character of the lesions. After two weeks of tartar emetic therapy, the vaginal lesions had practically disappeared, the cervical lesion was 90 per cent healed, and the stenotic condition of the vaginal vault was subsiding.

Tartar emetic therapy must be maintained for a period of several months to prevent recurrence of the disease.

CHORIONANGIOMA OF THE PLACENTA ASSOCIATED WITH LOW IMPLANTATION AND PREMATURE SEPARATION

DANIEL B. ROTH, M.D., TEANECK, N. J.

(From the A. S. F. Regional Hospital, Fort Benning, Ga.)

CHORIONANGIOMA of the placenta is a benign tumor arising from the chorionic mesenchyme. Whereas the chorionepitheliomas and hydatids arise from the epithelial elements and are relatively common, the chorionangiomas come from the chorionic stroma and are quite rare. The first case was reported in 1798 by John Clarke, and since that time 22 have appeared in the literature. They are known by many names. Virchow called them myxoma fibrosum chorii. Others call them hemangiomas. Beneke (1900) gave them the name of chorionangiomas. Their incidence has been variously estimated from 1 in 7,000 to 1 in 700, but Siddall in the routine study of 600 placentas found six small tumors.

Pathologically, there are three main types; cellular, vascular, and degenerative. Grossly they show considerable variation in size, and may be up to the size of the fetal head. They may be single or multiple, and always have a capsule or a pseudocapsule and are easily enucleated. They are usually on the fetal surface of the placenta, but may be marginal or buried in the placenta. The cellular type is a grayish red, while the vascular type is a deep bluish red. Microscopically they show considerable variation, but most commonly there is a loose groundwork of chorionic stromal cells, predominantly oval in shape, supporting numerous small blood vessels and capillaries. The vessels are usually dilated and filled with blood cells and lined with a single layer of endothelium.

Clinically these tumors are benign, but they may be associated with vaginal bleeding, hydramnios, and premature labor. If the tumors are large they may cause dystocia. In cases of hydramnios and premature labor the fetal mortality may run as high as 30 to 40 per cent.

The present case is reported because of the association of premature placental separation with chorionangioma.

The patient, a 38-year-old gravida vi, para v, was admitted to the hospital with a history of painless vaginal bleeding of seven hours' duration, three weeks prior to term. Her history during her pregnancy was uncomplicated; blood counts and urines were normal, and no toxic signs were present except elevation of blood pressure, which had been 150/86 during the first trimester and 130/78 in the latter months. The total weight gain was 22 pounds. She had had five uncomplicated deliveries in the past 13 years, all the babies being between 5 pounds, 6 ounces and 6 pounds, 6 ounces.

Examination on admission revealed a conscious and well-oriented female who was bleeding vaginally. Her temperature was 98.2° F.; pulse, 84; and respirations, 18. Heart and lungs were normal. Her blood pressure was 118/70. The abdomen was enlarged to the size of an eight-month pregnancy, fetus was in right occipitoanterior position with the fetal heart in the right lower quadrant. Her blood count on admission showed 4,100,000 red blood cells, and 80 per cent hemoglobin which was essentially what it had been during the prenatal course. However, with the history of bleeding a transfusion was deemed advisable, inasmuch as the amount of blood loss could not be accuratedly determined.

X-ray examination was done to determine the placental site, and the placenta was visualized on the posterior uterine wall in the middle and lower third. After 350 c.c. of blood had been given, the patient had a chill and the blood was discontinued (patient, a type O, was given type O blood).

During the transfusion the patient began to have uterine contractions, and at its conclusion she was taken to the delivery room and a vaginal examination done. The cervix was two fingerbreadths dilated and partially effaced, and no placental tissue was palpable through the os. The head was well engaged. About 200 c.c. of clots were found in the vagina, but active bleeding had ceased. Expectant treatment was decided upon, and a few hours later she was delivered spontaneously of a living male infant weighing 4 pounds, 8 ounces. Intravenous ergot was given after the birth of the anterior shoulder and the placenta was expressed without difficulty along with about 200 c.c. of clots. Following the expression there was little bleeding, and the patient was returned to her room in good condition. The placenta showed evidence of low implantation with the point of rupture only 5 cm. from the edge. Pathologic report was as follows:

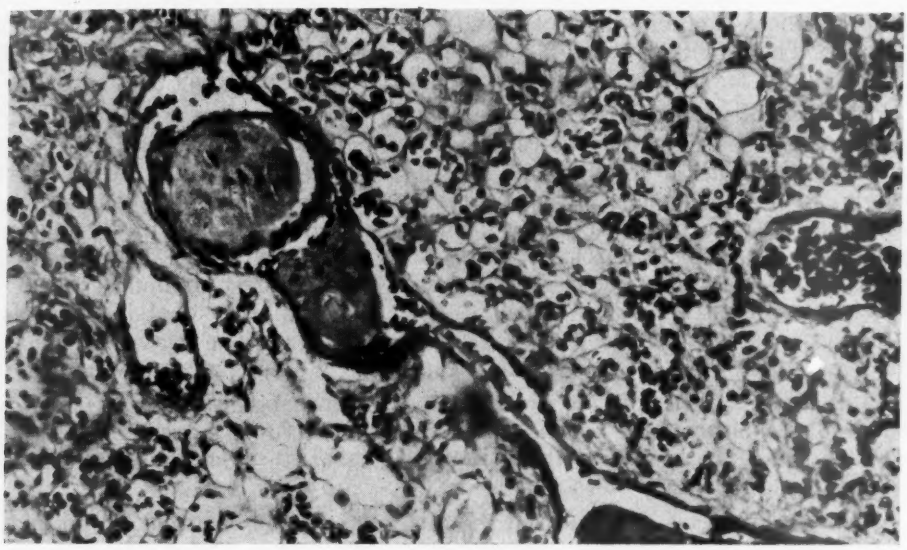


Fig. 1.

Gross: Specimen consisted of a mature placenta and adherent cord measuring about 60 inches in length. The placental membranes appeared to be normal and uniform in consistency. There was a small placenta succenturiate. The fetal surface appeared to be normal. The insertion of the cord was marginal. The maternal surface was made up of well-formed cotyledons. There were no defects in the continuity. The edge of the placenta close to the insertion of the cord showed an area which appeared to be degenerative in character and made up of white fibrous tissue. Adjacent to this was a large sinusoid which was thrombotic.

Microscopic: Several sections of tissue taken from the placenta showed a rather unusual picture characterized by the presence of masses of embryonic capillaries which formed large hemangiomas filled with considerable quantity of blood. Multiple hemorrhages were noted which extended into the supporting stroma. Numerous large sinuses with invading syncytial cells appeared to be somewhat larger than normal, tended to have arborizations, and were unusually

well vascularized. Many of the villi appeared to contain very little stroma, a layer of Langhan's cells formed the margin. The remainder of the villus was composed of one or more large venous sinuses.

Diagnosis: Chorionangioma of the placenta.

The patient made an uneventful recovery and remained well after leaving the hospital.

Comment

This case is of interest because it presents a combination of a highly vascularized, chorionangiomatous placenta in an abnormally located implantation. The combination of the two conditions undoubtedly was the cause of the premature separation and the premature labor. The slight elevation of systolic pressures acted in this patient's course may have been indicative of a mild toxemia, which would have played a part in the condition, but in the absence of any other signs this is open to question. There were no evidences of hydramnios in this case.

One can postulate that the common occurrence of premature labor in cases of chorionangioma is due to the action of these tumors as foreign bodies in the wall of the uterus, and that in this specific case, due to the abnormal implantation site and the increased vascularity of the placenta, bleeding occurred. Whether or not the changes in the placenta cause abnormalities in its function of producing progesterone and thus further the occurrence of premature labor is a matter for conjecture. I know of no endocrinologic studies in these cases to substantiate or deny this hypothesis.

References

1. Marchetti, A.: Surg., Gynec. & Obst. **68**: 733-743, 1939.
2. Fisher, J. H.: Am. J. Obst. & Gynec. **40**: 493-498, 1940.
3. Siegal, L. H., and Holley, E.: Am. J. Obst. & Gynec. **38**: 353-355, 1939.

836 Garrison Avenue.

PRIMARY CARCINOMA OF THE FALLOPIAN TUBE

MORTON VESELL, M.D., F.A.C.S., AND HARRY SCHNEIDER, M.D., F.A.C.S.
NEW YORK, N. Y.
(From the Beth Israel Hospital)

OF ALL the derivatives of the Müllerian duct, the Fallopian tube is least often affected by carcinoma, while the cervix is the most frequent. According to the literature, the incidence of primary carcinoma of the tube ranges from 0.34 per cent to 1.33 per cent of operations on diseased tubes. At Mount Sinai Hospital, New York, during the years 1928 to 1939, 8,356 patients were admitted to the gynecologic service, and only one case of primary carcinoma of the tube was seen. At Beth Israel Hospital, New York City, during the same eleven-year span, four unquestionable cases of primary carcinoma of the tube were seen.

The preoperative diagnosis of primary carcinoma of the Fallopian tube is very seldom made. Occasionally it has been suspected, and this purely on the sign of intermittent watery and serosanguinous vaginal discharge in women past the menopause. While this clinical feature is suggestive of malignancy of the tube it is by no means pathognomonic. As this condition usually occurs together with other pathology such as uterine fibroids, ovarian cysts, diseased adnexa, etc., it is almost impossible in most cases to single out carcinoma of the tube. However, it is felt that salpingography might be a decided aid in making a preoperative diagnosis of tubal malignancy. It is strongly urged that salpingography be used far more liberally in cases where tubal malignancy is considered. In the two cases to be reported the pathology was such that it is felt that the preoperative diagnosis of carcinoma of the tube might have been made had salpingography been utilized.

Case Reports

CASE 1.—Mrs. M. S., white, aged 53 years, was first seen on April 30, 1945, when she complained of abdominal fullness. She was a para iii, gravida iii, and had no miscarriages. Her youngest child was 24 years old. Her menses began at the age of 13 years occurred every twenty-eight days, and lasted five days. She had had her menopause at the age of 48, five years ago, and no further vaginal bleeding had occurred. Her present illness dated back to 1929, seventeen years ago, when she complained of abdominal fullness. At this time she was told by her local physician she had fibroids of the uterus. She was fairly well for fifteen years until late in 1944 when she again complained of fullness of the abdomen. There was no watery or serosanguineous vaginal discharge present. However, she did complain of malaise and loss of weight. In January, 1945, she again visited her local physician and was told her fibroids grew larger and she needed an operation. On her present admission to the hospital on April 30, 1945, she complained of a loss of 25 pounds in the last six months, and a fullness in the abdomen.

Physical Examination.—Patient looked slightly anemic, otherwise she appeared in good physical condition. Hemoglobin was 70 per cent; red blood corpuscles were 3,800,000; white blood corpuscles, 11,000; and her urine showed a specific gravity of 1020, 2 plus albumin, and no casts. The rest of the examination was negative except for the vaginal findings. The latter revealed an ir-

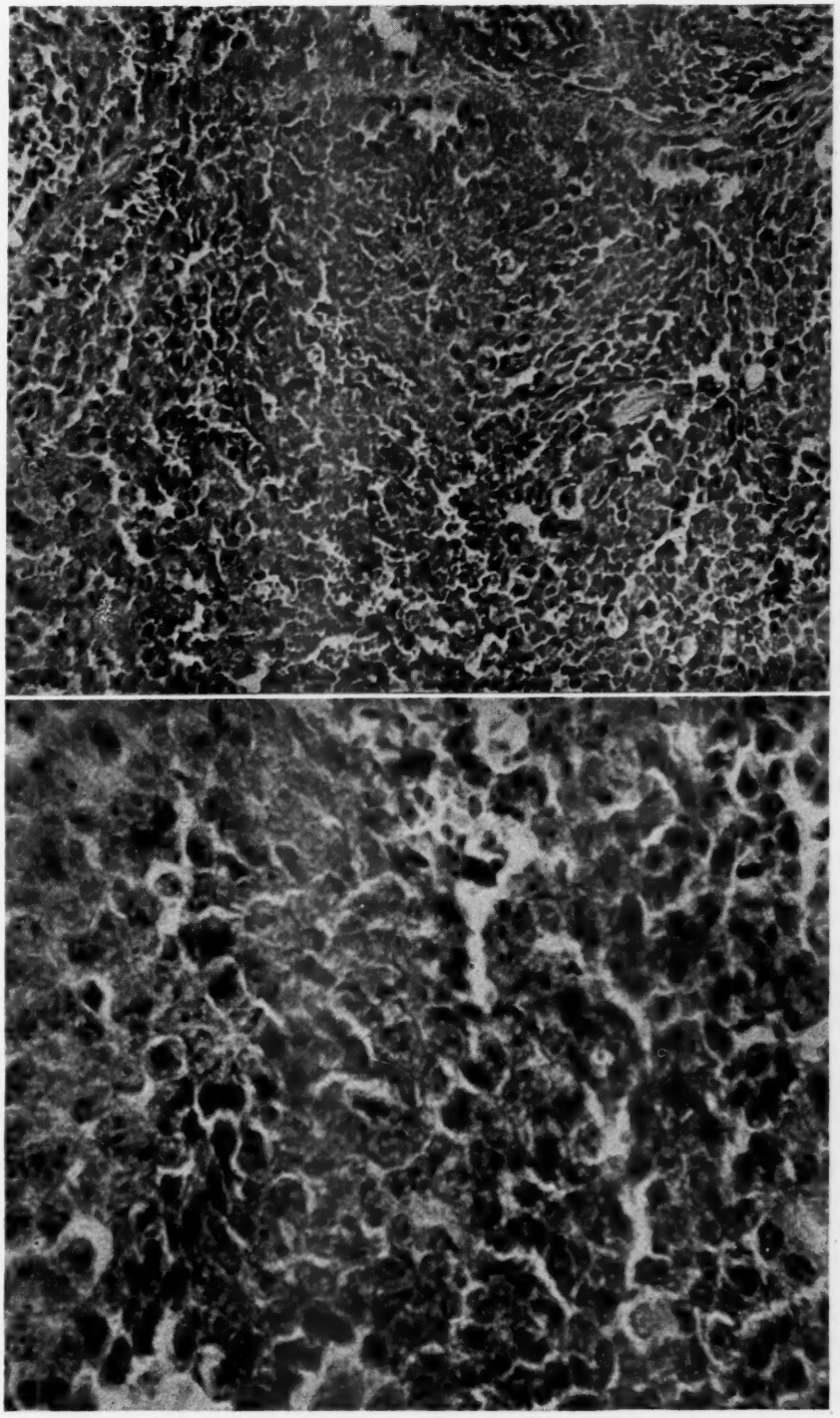


Fig. 1.—Case 1. Cross section of tumor, low power.
Fig. 2. Case 1. Same section, high power.

regular uterus reaching to three fingerbreadths above the symphysis pubis. To the right of the uterus and contiguous with it was a mass 6 by 6 by 3 cm. which was thought to be a fibroid. The cervix and uterus were freely movable.

Operation.—The patient was operated upon on May 1, 1945, and a myomatous uterus about the size of a 12 weeks' gravidity and a markedly thickened sausage-shaped right Fallopian tube was found. The latter was freely movable, as was the uterus with its fibroids. There were no apparent adhesions or metastasis. A total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed, as the tubal mass was considered malignant, grossly. The patient made an uneventful recovery and was discharged on the twelfth postoperative day.

Pathology.—Gross: The uterus was 9.5 cm. long and 5 cm. wide, and contained several almond-sized fibroids. The uterine cavity contained a small polyp 1.2 cm. long. The right tube was elongated. The thin portion of the tube, from tubal angle to the tortuous portion, measured 6.5 cm. The tortuous part was 5 cm. long, 2.5 cm. wide, and 2 cm. thick, and rather solid in consistency. The surface of the thickened area was yellowish with irregular protrusions. On cut section the tortuous portion of the tube was entirely solid and contained homogenous tumor masses.

Microscopic Examination: Revealed an anaplastic solid papillary carcinoma of the right tube. Mitotic figures were numerous. Carcinoma was not found in the uterus, ovaries, or left tube.

Subsequent course.—The patient felt well for about one year and then complained of abdominal fullness. Examination at this time, April, 1946, disclosed a tender mass 4 by 4 by 3 cm. at the scar of the vaginal vault. Deep x-ray therapy was given.

In the latter part of June, 1946, she was seen again and the mass felt on previous examinations was larger. She complained of some vaginal bleeding. She continued to run a downhill course and died August 1, 1946.

CASE 2.—Mrs. E. L., white, aged 61 years, complained of vaginal bleeding of three years' duration. She was a para i, gravida ii, and had had her menopause fifteen years ago. Seventeen years ago she had an appendectomy, three years ago a dilatation and curettage, and three months ago a cholecystectomy. The previous curettage revealed a secretory endometrium with insufficient tissue for diagnosis. At the time of the cholecystectomy a tumor of the right ovary was noticed. Her present complaint was vaginal bleeding. This was mild in character and intermittent during the past three years.

Physical Examination.—The patient was a rather obese white female whose general examination was essentially negative except for vaginal examination. External genitals were normal. Vaginal outlet was narrow. The uterus was small, freely movable, but pushed to the left by a mass 6 by 8 by 3 cm. The latter was firm, tender, and somewhat fixed. A diagnosis of ovarian malignancy was entertained.

Laboratory Data.—Urine was negative. Her blood count showed 4,000,000 red cells; hemoglobin, 67 per cent; white cells, 8,000. Sedimentation rate was 52 mm. per hour. Wassermann was negative.

Operation.—On July 17, 1945, a total abdominal hysterectomy and bilateral salpingooophorectomy were performed under spinal anesthesia. The right adnexus was the site of a tubo-ovarian mass adherent to the cul-de-sac. The left tube was somewhat dilated, while the uterus was essentially normal. Her postoperative course was uneventful, and she was discharged on the seventeenth postoperative day.

Pathology.—Gross: A pear-shaped firm right tube was present. No traces of abdominal ostium were present. On long section only its outer layers can be

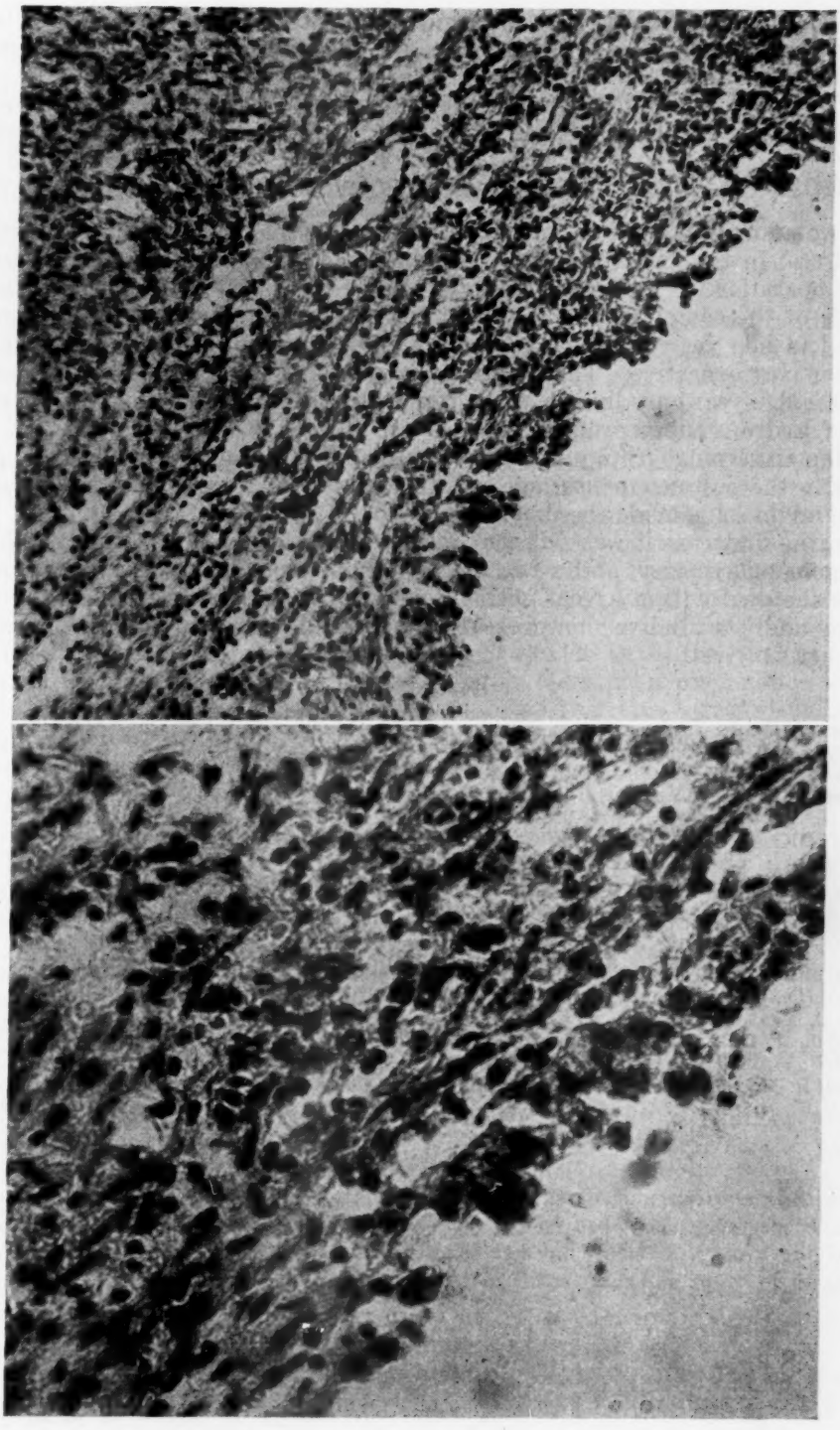


Fig. 3.—Case 2. Cross section of tumor, low power.
Fig. 4.—Same section, high power.

recognized as tube wall. The remainder consisted of pinkish and yellowish homogenous masses. The other tube was a hydrosalpinx 6.4 cm. by 1 cm. A moderate-sized uterus with nothing remarkable was apparent.

Microscopic: Section through the outer third of the right tube revealed a widely necrotic adenocarcinoma. The other tube was an atrophic hydrosalpinx.

Summary and Conclusion

Two additional cases of primary carcinoma of the Fallopian tube, both unilateral and in the right tube, are herein reported. Neither case was diagnosed before operation. The proper therapy was executed, and yet the first patient, in spite of the completeness of operation and x-ray treatment in addition, succumbed in one year. The second patient is still alive and well, but it is only one year post operative. The literature reveals only an occasional case that survived the five-year cure limit. Neither of these cases gave a history of the symptoms of hydrops tubae profluens.

Hysterosalpingography should be utilized more often in cases of pelvic masses in the postmenopausal age group. In both of these cases, the above procedure might have made the diagnosis preoperatively.

In the first case it was felt that the total abdominal hysterectomy, bilateral salpingo-oophorectomy, and x-ray therapy should have produced a cure, nevertheless she died within a year. The second patient had not received any x-ray therapy and is still alive; however, it is too early to make any definite comments about her survival.

References

Danreuther, W. I.: Am. J. Obst. & Gynec. **30**: 724, 1935.
Vest, C. W.: Bull. Johns Hopkins Hosp. **25**: 305, 1914.
Wechsler, H. F.: Arch. Path. **2**: 161, 1926.
Wharton, L. R., and Krock, F. H.: Arch. Surg. **18**: 848, 1929.
Fullerton, W. D.: Am. J. Surg. **48**: 467-472, 1940.
Martzloff, K. A.: Am. J. Obst. & Gynec. **40**: 804-821, 1940.
Baron, H. A.: Canad. M. A. J. **43**: 118-121, 1940.
Wilson, H.: Roy. Melbourne Hosp. Clin. Rep. **11**: 44-46, 1940.
Platz, J.: Arch. f. Gynäk. **170**: 604-615, 1940.
Mallory, T. B.: New England J. Med. **224**: 427-28, 1941.
Tuta, J. A., and Stuhr, W. A.: Am. J. Clin. Path. **11**: 864-870, 1941.
Hoenig, E., and Warner, M. P.: M. Rec. **155**: 271-273, 1942.
Baker, J. O., and Blais, A.: Canad. M. A. J. **46**: 67-68, 1942.
Hobbs, J. E.: South. M. J. **35**: 733-737, 1942.
McGolrich, J. L., Strass, H., and Rao, J.: Am. J. Surg. **59**: 555-562, 1943.
Rosenthal, M., and Peterson, K.: Arizona Med. **1**: 247-249, 1944.
Mitchell, R. M., and Mohler, R. W.: Am. J. Obst. & Gynec. **50**: 283- 292, 1945.
Ayre, J. E., Bauld, W. A. G., and Kearns, P. J.: Am. J. Obst. & Gynec. **50**: 196-202, 1945.

Addendum

Since this article was submitted, Mrs. E. L. (Case 2), has developed metastases in the pelvis. Biopsy specimen taken from a mass in the vaginal vault revealed carcinoma. She is receiving x-ray treatment, but her condition is poor. This confirms our opinion that these cases do badly, and that the diagnosis must be made still earlier.

A NEW MULTIPURPOSE APPARATUS FOR USE IN THE DIAGNOSIS AND TREATMENT OF STERILITY IN THE FEMALE*†

ABNER I. WEISMAN, M.D., NEW YORK, N. Y.

IN THE past twenty-five years much progress has been made in the diagnosis and treatment of female sterility. This is especially true with regard to sterility originating in the genital tract. In surveying and evaluating the reproductive tract of the female, three separate and distinct schools of approach have been evolved. Headed respectively by Rubin,[1] Jarcho,[2] and Stein,[3] each group advocates a different method of diagnosis. Since 1920 Rubin and the men who adhere to his teaching have used carbon dioxide insufflation almost exclusively. Later, with the development of innocuous radio-opaque substances, Jarcho and his followers felt that uterotubal x-ray visualization was the method of choice in evaluating disorders of the female genital tract. Finally, Stein and his somewhat smaller group have reported that the most valuable diagnostic procedure in female sterility is the combined technique of gas insufflation *together with* uterotubal x-rays. Stein instills carbon dioxide as in the ordinary tubal test, then allows large amounts of gas to enter, causing a pneumoperitoneum. Finally, he injects the radio-opaque substance and obtains x-ray visualization. By this combined contrast method most excellent visualization of all the pelvic organs (including the ovaries) can be obtained.

Each of the above-mentioned three procedures is a valuable diagnostic agent and each has its place in gynecology depending upon the individual patient and the presenting problems.

It is not within the province of this short paper to expound the well-known virtues of any particular one of the three procedures. Medical discussions of the "pros" and "cons" of each method will probably go on for decades. The purpose of this paper is simply to introduce a new apparatus, the "Gynograph," so constructed that the physician has the facility to perform with this single mechanism whichever one of the above-mentioned tests he desires. He may also perform all three tests simultaneously. This compact apparatus is believed to be a highly efficient portable instrument for either office, clinic, or hospital work.

After seven years of extensive trials the gynograph was finally evolved. And while its facilities are multiple, its dangers are minimal to the patient. For example, in 1,100 tests performed by the author over the seven-year period, the apparatus has been highly satisfactory clinically. It is interesting to note that, owing to the safety factors of the instrument, not one serious mishap resulted.

The mechanical principle employed in the gynograph consists essentially of a completely closed gaseous circuit which is constantly under manometric control and in which carbon dioxide, under pressure, is the motivating force. Thus, not only can carbon dioxide be insufflated, but in addition the same source of carbon dioxide is used as the vis a tergo for the instillation of the radio-opaque oil.

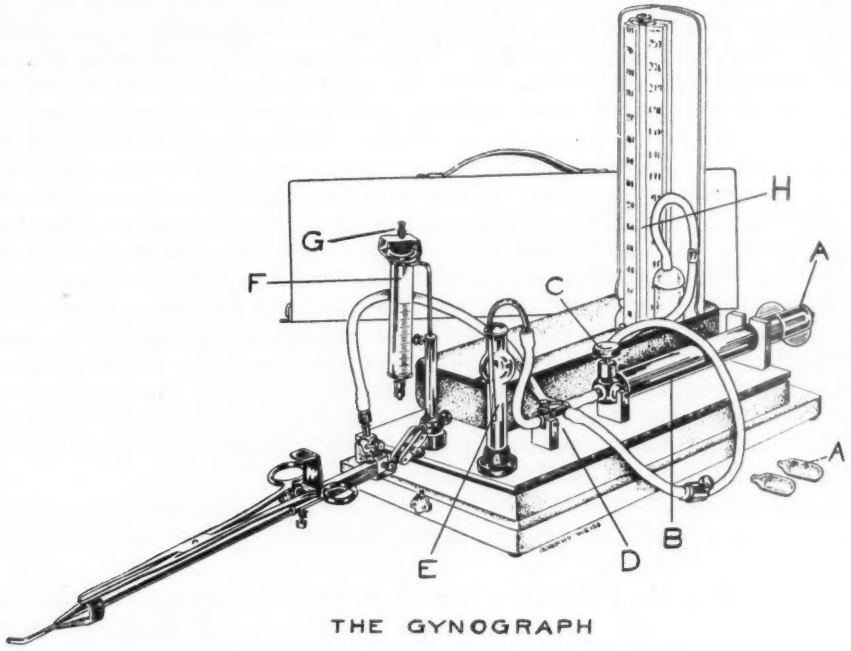
---

*Presented before the Clinical Society of the Jewish Memorial Hospital, New York, N. Y., Jan. 7, 1947.

†With the technical assistance of Mr. John L. Marco of Goodman-Kleiner Co., New York, N. Y.

Technique

The patient is placed in lithotomy position on the x-ray table. Then a specially devised self-retaining cannula (which itself is an incorporated part of the gynograph) is introduced into the cervical canal. The cannula presents a number of new features including a rotating tip, a revolving acorn, a tenaculum-grasping device and an end-piece which connects directly to the gynograph. After the cannula is secured the patient can assume a more comfortable supine position with legs extended. The gynograph is then placed on the x-ray table between the patient's legs and connected directly to the indwelling cannula.



THE GYNOGRAPH

Fig. 1.

The source of carbon dioxide is a very small inexpensive cartridge similar to one used in producing artificial carbonated water. The gas, released from the cartridge (*A*) by a small piercing device, flows into a cylindrical expansion chamber (*B*). As the gas expands, the pressure decreases so that it is completely under control of the main valve (*C*). By a slow counterclockwise turn of this valve the gas escapes. Before allowing the carbon dioxide to enter the patient, the rate of flow is established and predetermined by shunting the gas bubbles (by means of a two-way valve) (*D*) into an outlet-counting chamber containing water (*E*). A rate of flow of from 60 to 80 bubbles per minute, or less, is essential for safety. After the rate of flow has been established, the two-way valve is released and the gas is then allowed to flow slowly into the patient through the cannula under manometric observation. From this point on the determination of tubal patency and gaseous entrance into the peritoneal cavity is similar to that of the Rubin test, i.e., with a drop in manometric pressure, tubal patency can be said to exist. The test can be repeated as often as necessary by simply releasing the carbon dioxide into the water chamber and starting over again. If tubal patency is established and a pneumoperitoneum desired, the gas can be allowed to flow into the abdominal cavity for three to five minutes or longer, if necessary, at the same rate of gas flow (60 to 80 bubbles per minute).

Finally, for uterotubal x-ray visualization an ordinary 10 c.c. syringe containing 5 c.c. of a radio-opaque oil, already set up on a rack (*F*), is swung over and inserted into the cannula. The gas is then directly connected to an adapter attached to the top of the syringe (*G*), completing the circuit once more. Under direct carbon dioxide pressure (up to 200 mm.), the oil is forced through the cannula into the uterus and tubes. As the oil enters, x-ray pictures are fractionally taken in the usual manner. During the entire process of tubal insufflation and hysterosalpingography, the hands of the operator are entirely free for fluoroscopy, etc. (The manometer [*H*] and other parts of the instrument are prepared with a luminous paint for use in the dark room.)

In this paper it is not necessary to go into the details of the preliminaries to tubal testing, such as complete vaginal examination, blood sedimentation rate, premedication, local preparation, etc. These important preliminary steps should be employed here with the same care and precaution as they would be in the ordinary Rubin test or hysterosalpingography.

Summary

A new instrument, the "Gynograph," for use in evaluating the status of the female genital tract in sterility studies, is presented. With this single apparatus, tubal carbon dioxide insufflation, uterotubal x-rays, and pelvic viscerography can be performed easily.

In the author's hands this simple compact portable device has proved highly satisfactory in 1,100 clinical tests.

References

1. Rubin, I. C.: J. A. M. A. **75**: 661, 1920.
2. Jarcho, J.: Surg., Gynec. & Obst. **45**: 129, 1927.
3. Stein, I. F.: Radiology **15**: 83, 1930.

PAINLESS LABORS FOLLOWING PRESACRAL NEURECTOMY

GEORGE BLINICK, M.D., NEW YORK, N. Y.
(From the Gynecological Service of Beth Israel Hospital)

THE following report is that of a patient who underwent presacral neurectomy for dysmenorrhea in 1941 and had painless labors associated with uterine inertia in 1942 and 1944. No similar case of such profound uterine inertia and abolition of labor pains has been reported following presacral neurectomy.

Cases of pregnancy following presacral resection indicate that there is no interference with the normal progress of labor. The first stage is generally agreed to be relatively painless, but no difference in the intensity or frequency of pain has been noted in the second tage.[1]

Cotte[2, 3] stated that in more than fifty patients who had had resection of the superior hypogastric plexus no effect was noted in subsequent parturition.

Davis[4] reported two cases in whom labor was precipitate and relatively painless.

Wetherell[5] described the case of a patient who became pregnant thirteen months after operation. Labor pains were irregular, weak, and confined to the back. She had no pains in front. The position was right occipitoposterior. The first stage was conducted under morphine and scopolamine and lasted eighteen hours. The second stage lasted five hours and was terminated by Scanzoni rotation and forceps extraction.

Donaldson[6] observed three patients who became pregnant after operation and states that the "labor pains were the same as in an ordinary patient."

Reed[7] in two patients found no change in nidation, pregnancy, and parturition, although in one cesarean section was done for kidney failure and a fibroid uterus.

Pearce[8] cited the case of a 20-year-old girl who was delivered of a 9½-pound baby in 1932 after six days of labor. In 1937 presacral neurectomy was done. In 1938 she delivered an 8½-pound baby in 1½ hours with only three hard pains. He states "that in some patients, probably only a small proportion, the first stage of labor is painless and rapid or else unobserved."

Spackman,[9] in a series of 100 operations, had records of nine patients who subsequently gave birth to twelve children. Labor was less painful, especially in the first stage; the labor mechanism was not altered.

Hendrick[10] reported two cases each of whom had two normal pregnancies.

Rutherford,[11] in a careful analysis of eight cases who had obstetric follow-up, found no disorder of function as a result of the operation. Labor pains were absent during the first stage of labor in five of the eight cases. Pain was absent during the greater portion of the first stage in two other cases. It was found that the duration of labor may be somewhat shortened.

Salgado[12] reported an easy short labor four years after presacral neurectomy.

Case Report

Mrs. A. R., a 25-year-old housewife, was first seen on Feb. 1, 1941. Her menses had begun at 14 years of age, were regular every twenty-eight days, and lasted four to five days. The flow was moderate in amount. She had had

premenstrual cramps since the onset of her periods which had become progressively more severe, especially in the past four years. In the past year, the pain was much more intense and began five days after the completion of a period and continued up to the onset of the next period. Medical measures including various forms of endocrine therapy were unsuccessful in relieving her pain. She had had an appendectomy elsewhere five years ago. She had never been pregnant.

There was a right, well-healed pararectus scar. There was moderate tenderness throughout the lower abdomen, but no masses or rigidity were felt. Vaginal examination disclosed a marital introitus. The cervix was normal. The uterus was slightly enlarged, irregular, and contained small fibroid nodules. The left ovary measured 3 by 4 cm. in size. On Feb. 25, 1941, at laparotomy, the uterus was found to contain numerous superficial fibroid nodules measuring from a few mm. to 3 cm. in size. The left ovary was cystic. A presacral neurectomy, multiple myomectomies, and resection of the left ovary were performed. The postoperative course was uneventful except for retention of urine for the first two postoperative days.

She became pregnant seven months later and labor began on the expected date of delivery June 25, 1942. At 12:30 P.M. she complained of frequency of urination and fullness in the lower abdomen, and the cervix was found to be two fingerbreadths dilated with a slight bloody show, although there had been no back or lower abdominal pain. The fetus was engaged in the right occipitoanterior position, and was smaller than usual. Uterine contractions were weak, painless, transient, and ineffectual, despite the administration of castor oil, a hot enema, and three doses of quinine sulfate (grains V). The following morning, at 5:30 A.M., there had been no progress and 2 minims of thymophysin were given. It was felt that the uterine scars were small and superficial and that there was little danger of uterine rupture.

Uterine contractions occurred every five minutes and lasted thirty seconds and were painless. At 7:30 A.M. the contractions were again weak and irregular, and 3 more minims of the thymophysin were given causing moderate augmentation of contractions for the next hour. At 1:00 P.M., the cervix was three fingerbreadths dilated and uterine contractions were again weak and ineffectual. Pantopon grain $\frac{1}{3}$ and scopolamine grain $\frac{1}{500}$ were given in an attempt to hasten cervical dilatation and not because of any discomfort felt by the patient. Two hours later 2 minims of thymophysin were given and contractions occurred every three minutes and lasted thirty seconds. At 3:12 P.M. the membranes ruptured spontaneously.

At 3:30 P.M., she was fully dilated and, following the administration of an additional 3 minims of thymophysin hard contractions occurred every two minutes and lasted for sixty seconds until delivery. She was encouraged to bear down with each contraction since she did not have any spontaneous impulse to do so.

During the entire labor she had not experienced any pain even when the uterus underwent frequent firm contractions following the administration of thymophysin. At 4 P.M., the head crowned the perineum and she complained of pain for the first time during the entire first and second stages of labor. At 4:10 P.M., she was given gas, oxygen, and ether anesthesia. An episiotomy was performed and a female child weighing 5 pounds was born spontaneously at 4:13 P.M. The placenta was expelled at 4:30 P.M. The total duration of labor was twenty-eight hours and thirty minutes. The postpartum course was uneventful and she was discharged nine days after delivery.

Her second delivery was on Feb. 3, 1945, and was in all respects similar to the first already described, except that the onset of labor was initiated by the

spontaneous rupture of the membranes on Feb. 2, 1945, at 3 P.M., and weak painless ineffectual contractions were noted. After twenty-four hours of weak irregular ineffectual cramps, small repeated doses of thymophysin caused moderately strong uterine contractions, and she was delivered at 7 P.M. spontaneously of a 6 pound, 11 ounce boy. Again no pain was experienced until the head distended the perineum. The total duration of labor was twenty-nine hours and twenty-three minutes. The postpartum course was uneventful.

At the present time she feels well and is menstruating regularly every 28 to 30 days for four days. She occasionally has slight lower abdominal discomfort and distention on the day prior to menstruation, but has no actual cramps or pain. Her uterus is slightly enlarged and irregular.

Comment

The actual and theoretical effects of presacral neurectomy upon labor cannot be understood without a knowledge of the innervation of the uterus. Unfortunately, there is considerable confusion both as to the anatomic pathways and physiologic mechanisms involved. "All existing evidence points to the fact that the nerves to and within the uterus are not essential for parturition."[13-15] However, the fact that labor can take place independently of the extrinsic uterine innervation does not mean that nervous impulses do not influence, at least in part, normal uterine motility and perception of pain. The presacral nerve contains both sensory and motor fibers to the uterus, whereas the cervix, vagina, perineum, and pelvic floor are supplied through independent pathways,[16] The presacral nerve lies above the promontory of the sacrum and is inconstant in morphology. It may vary fom a single or double strand to multiple and diffusely separated nerve filaments.[17, 18]

If this anatomic description is correct, then complete excision of the presacral nerve should theoretically interrupt both sensory and motor impulses to the uterus, and result in painless laobr and some degree of uterine inertia, as described in the case reported here. On the other hand, the normal pattern of contractility of the uterine musculature is probably controlled by endocrine factors and distention of the uterus, and is only partially dependent upon the extrinsic nerve supply. That the latter does play some role is best demonstrated by clinical experiments with caudal anesthesia. Peridural block extending to the eleventh thoracic root (where the sensory fibers originate which course through the presacral nerve) abolishes the pain of uterine contractions without abolishing their force.[19] Extending the block to the fourth thoracic segment of the cord or higher (where the motor fibers originate which course through the presacral nerve) significantly impairs the strength of uterine contractions in 69 per cent of patients.[20] In fact, caudal anesthesia at this level has been utilized to arrest premature labor to the delay of several weeks.[16]

Why alterations in labor to the degree experienced by this patient have not been previously described following presacral neurectomy cannot be answered. Furthermore, since this operation does not interrupt the innervation of the cervix and vagina, it is difficult to understand why the pain of cervical distention was abolished.

It is obvious that many factors beside those of innervation, such as size of the child, mechanism of descent, sensibility of the patient, etc., modify the pain and force of uterine contraction. It is possible that in this patient a favorable anatomic disposition of the plexus may have resulted in a more thorough excision than that ordinarily obtained; it may be that she was predisposed toward primary uterine inertia as a result of fibroids, uterine scars, or a hypothetical endocrine factor. The complete absence of pain even at the

height of a thymophysin-induced uterine contraction during both first and second stages would seem to indicate that the operation played a significant role in the production of the painless labor and the associated uterine inertia.

Summary

1. A case in which two painless labors associated with primary uterine inertia occurred following presacral neurectomy is described. Pain was experienced only when the perineum was distended by the crowning head. No similar case of such profound uterine inertia and abolition of labor pains has been reported following resection of the superior hypogastric plexus.

2. Interruption of the innervation of the uterus by presacral resection may abolish the pain and force of uterine contractions in some patients, although it is well known that the extrinsic nerves are not essential for parturition.

References

1. Collins, C. G.: New Orleans M. & S. J. **91**: 75, 1938.
2. Cotte, G.: Zentrabl. F. Gynäk. **57**: 2252, 1933.
3. Cotte, G.: Am. J. Obst. & Gynec. **33**: 1034, 1937.
4. Davis, A. A.: Brit. M. J. **2**: 1, 1934.
5. Wetherell, F. S.: Am. J. Obst. & Gynec. **29**: 334, 1935.
6. Donaldson, M.: Proc. Royal Soc. Med. **29**: 947, 1936.
7. Reeb, M.: Gynecologie, **36**: 617, 1937.
8. Pearce, T. V.: Brit. M. J. **1**: 87, 1940.
9. Spackman, W. C.: Brit. M. J. **1**: 637, 1940.
10. Hendrick, J. W.: Texas State J. Med. **37**: 26, 1941.
11. Rutherford, R. N.: West. J. Surg. **50**: 597, 1942.
12. Salgado, C.: Rev. de ginec. a d'obst. **1**: 368, 1944.
13. Reynolds, S. M. R.: Physiology of the Uterus, New York, 1939, Paul B. Hoeber.
14. Davis, A. A.: Proc. Roy. Soc. Med. **29**: 931, 1936.
15. Ivy, A. C., and Danforth, D. N.: International Abst. Surg. **69**: 351, 1939.
16. Lull, C. B.: Control of Pain in Childbirth, Philadelphia, 1945, J. B. Lippincott Co.
17. Weinstein, B. B.: Surg., Gynec. & Obst. **74**: 245, 1942.
18. Labate, J. S.: Surg., Gynec. & Obst. **67**: 199, 1938.
19. Hineson, R. A., and Edwards, W. B.: J. A. M. A. **123**: 538, 1943.
20. Frankel, D. S.: Surg., Gynec. & Obst. **80**: 66, 1945.

55 East 86th Street

Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

Review of New Books

Gynecology

I. C. Rubin's **Uterotubal Insufflation**[1] is a comprehensive report of his diligent and productive activities in connection with sterility problems during more than twenty-five years.

Part I comprises a discussion of the gross and microscopic anatomy, the pathology, and the physiology of the Fallopian tube. Attention is directed to the fact that the length of the tube as determined by salpingography is considerably greater than is apparent during pelvic laparotomy or after extirpation, the difference being as much as 7 cm. or more, attributable to the stretching force of the injected opaque medium and to intrinsic peristalsis. Other anatomic points receiving proper emphasis are (1) that while the diameter of the tube lumen throughout its outer four-fifths readily admits the passage of a uterine sound, only the finest filiform bougie can with difficulty be threaded through the isthmic and intramural segments; (2) that while the relatively few longitudinal folds of the mucous membrane create a simple histologic pattern throughout the narrower segment of the lumen, they multiply distally to such an extent as to produce a strikingly beautiful and complicated labyrinthian arrangement; (3) the existence of both ciliated nonsecretory and nonciliated secretory epithelium, the former greatly predominating throughout the fimbriated segment and both undergoing cyclic variations; (4) that the muscular layer of the tube wall is considerably thicker in the isthmic segment so that it imparts to the palpating finger the sensation of a solid cord easily mistaken for pathologic infiltration; and (5) the existence of a narrow zone corresponding to the intramural segment which is capable of alternate contraction and dilatation like a true sphincter. Exhaustive roentgenologic studies of normal tubes in living human and animal subjects enabled the author to correct false conclusions drawn from similar studies on extirpated specimens that had undergone rigor mortis. These are considered in detail.

The chapter on pathology of the tubes discusses adequately the congenital and acquired causes of occlusion. Statistical studies, including the author's large experience, on the site of tubal occlusions with reference to the two ends of the tubes, vary considerably. In general, impaired tubal physiology resulting from puerperal infections is more easily restored to normal than when due to gonorrhea, since the latter often results in hydrosalpinx with permanent loss of both the ciliated epithelium and peristalsis. The author adopts a hopeful attitude toward greater success in plastic resections of occlusions at the uterine end with reimplantations through improvements in technique fortified by judicious physio- and chemotherapy, together with tubal insufflation.

In his chapter on physiology of the Fallopian tubes, he reveals the thoroughness and diligence with which he has pursued his investigations in an exhaustive objective and scientific study of this problem. With commendable ingenuity he has utilized uterotubal insufflation, hysterosalpingography with viscorayopaque, hippuran, lipiodal, etc., as well as kymographic records both in animal experiments and on human subjects. By such studies he has convincingly demonstrated tubal peristalsis and antiperistalsis, the exist-

[1] **Uterotubal Insufflation.** By I. C. Rubin, M.D., Clinical Professor of Gynecology, College of Physicians and Surgeons, Columbia University. With 159 illustrations, including 4 in color. 453 pages. The C. V. Mosby Company, St. Louis, 1947.

ence of an uterotubal sphincter and its influence on pressures, a well as a number of other interesting phenomena. He found the force of uterine contractions in the nonpregnant state to average between 0.3 and 0.5 mm. Hg to 1.5 mm. Hg as compared with a range of 30 to 40 mm. Hg exhibited by the tubes.

Chapter IV is devoted to a study of the relation of ovarian function to the physiology of the Fallopian tubes. While not uniform or constant, there appears to be a moderate relative increase in uterotubal tone during the midinterval. The exact time of ovulation in women has not yet been accurately determined. Diminished uterotubal tonus as well as of the rate and amplitude of tubal contractions is found with hypofunction of the ovaries. The menopause produces a striking loss of tonicity and constant fatigability of the tubal muscle which, however, can be restored by the injection of follicle-stimulating hormones.

Part II comprises five chapters devoted to the technique of tubal insufflation and its diagnostic application. The prime object of the procedure is, of course, determination of tubal patency or nonpatency as a factor in sterility problems. As special indications the author lists:

1. (a) Primary sterility when all other factors can be excluded; (b) sterility attributable to prior gonorrheal pelvic infection but without signs of activity for six months and with no demonstrable infection present; (c) primary sterility with a history of previous peritonitis of appendicular origin; (d) secondary infection attributable to puerperal sepsis; and (e) cases of one-child sterility.

2. To determine the advisability and type of operation designed for the relief of sterility. He points out that operations upon the cervix for sterility, curettage, and myomectomy for sterility should always follow and never precede insufflation.

3. To determine the condition of a residual tube following unilateral salpingectomy.

4. As a therapeutic measure for tubal sterility.

As secondary indications the author recommends insufflation (1) as a guide during operations for tubal sterility to locate accurately the obstruction and determine its successful correction; (2) to determine the results of salpingoplasty; (3) to test the success of tubal sterilization, by the Madlener or Pomeroy technique. He cautions that here slow insufflation with pressures not exceeding 100 mm. Hg should be used; (4) to produce pneumoperitoneum for radiographic diagnosis of pelvic disease; (5) to relieve dysmenorrhea; (6) to determine the necessity for contraception; and (7) to study the physiology, anatomy, and pathology of the tubes.

As contraindications to uterotubal insufflation he emphasizes (1) the presence of inflammation of the genital tract; (2) menstruation; (3) genital bleeding, because of the possibility of gas embolism; (4) pregnancy; and (5) severe constitutional diseases that contraindicate pregnancy.

He considers the optimum time for insufflation to be the week following a regular period, and enumerates sound and convincing reasons in support of this opinion. His apparatus and its use as an office procedure is pictured and described in detail, together with interpretation of the findings and a discussion of shoulder pains, their cause and management.

In normally patent tubes during insufflation, the mercury column undergoes an initial rise of at least 30 to 40 mm. Hg and oftener between 50 and 100 mm. Hg, then drops abruptly 20 to 40 or more points and fluctuating only slightly during the remainder of the test. In a series of 3,200 sterility cases less than 50 per cent had normal patency and function. Much additional statistical data culled from the author's large and varied experience is recorded with interesting and illuminating discussions. Pressure readings is nonpatent tubes and the technique of localization of the site of obstruction are clearly presented; also, an intensive study of obstructions due to peritubal adhesions, tubal strictures and uterotubal spasm, with a record of ingenious animal experiments imitating by mechanical devices these types of occlusion with analysis of the author's statistics in this category, is given.

An interesting chapter is devoted to a discussion of tubal occlusion of nonvenereal origin, e.g., appendicitis, induced abortion, and ectopic pregnancy, with the incidence of pregnancy following insufflation as a therapeutic measure in this group.

Part III is devoted to a detailed discussion of the therapeutic application of insufflation both in primary and secondary sterility and its relationship to other sterility factors. The use of the kymograph in these studies the author regards as indispensable, and the value of insufflation during operations on the uterus and tubes designed to correct pathological occlusions is stressed. In the author's series he reports that of 517 women who became pregnant after insufflation, 419 had 490 full-term babies, and he tabulates 1,037 pregnancies that have followed insufflation in the hands of 65 other workers in this field.

Part IV comprises Chapters 12 and 13, in which are presented a detailed comparison of the diagnostic and therapeutic aspects of insufflation and lipiodol injection, as well as the incidence of complications and sequelae following both methods. Collective reports on 9,821 lipiodol injections showed 17 infections, while in approximately 10,000 insufflations reported by 14 different authors, no complications occurred. The author concludes that since both tubal obstruction and the two important points at which it occurs can be determined by single or repeated insufflation, "it is not necessary to resort to uterosalpingography in order to prognosticate the chances of success of a contemplated corrective operative procedure on the tubes."

Part V includes an historical review of the early use of solutions to determine tubal patency, the modifications of the author's apparatus that gradually evolved from the first model, and of the various gases that have been employed. A brief section is devoted to the treatment of dysmenorrhea by insufflation and another to the application of pneumoperitoneum to gynecology. There is also a complete tabulation of data obtained from a questionnaire circulated among colleagues on two occasions by the author. More than 3,000 of these were distributed, and 356 replies that could be used were received. In Table XXXIV are grouped the replies containing the most complete data. Here the total number of cases insufflated was 41,094. Patent tubes were found in 58 per cent, nonpatent tubes in 30 per cent, partially patent tubes in 7 per cent, and spasm in 5 per cent. In this group 7,407, or 18 per cent, became pregnant, 746 occurred within one month, and 809 within two months. In the same group seven embolisms occurred, of which six recovered and one died. All of these were due to the use of air or oxygen. There were no other deaths from insufflation when carbon dioxide was used. Next, the author's demonstration model for uterotubal insufflation is pictured and described. And, finally, there is a brief discussion of application of uterotubal insufflation to bovine and breeding mare sterility.

Certainly no one is as well fitted to write a book on uterotubal insufflation as is I. C. Rubin, and he has done a good job. The method is his own brain-child and his book reveals the immense amount of diligent effort, ingenious research, and clinical application he has contributed to its full fruition over the past quarter of a century. It is safe to assert that during this period no more valuable contribution has been made by anyone to the solution of sterility problems. The book contains a wealth of interesting and illuminating detail, the style is clear and concise, the illustrations are reasonably good, and there is appended a long list of references, and an adequate index. The author is to be congratulated upon the thoroughness and uniform excellence of his sterility work, and his book deserves a place in the library of every doctor who is engaged in the solution of sterility problems.

EDWARD H. RICHARDSON.

In **Progress in Gynecology,** Meigs and Sturgis[2] have edited seventy articles dealing with practically all phases of this specialty. The distinguished list of contributors was

[2]**Progress in Gynecology,** Edited by Joe V. Meigs, M.D., Clinical Professor of Gynecology, Harvard Medical School; Chief of the Vincent Memorial Hospital, the Gynecological Service of the Massachusetts General Hospital; Surgeon, Pondville Hospital; Gynecologist, Palmer Memorial Hospital, and Somers H. Sturgis, M.D., Chief, The Vincent Memorial Hospital Laboratory; Assistant Surgeon, Massachusetts General Hospital, 533 pages, illustrated. Grune & Stratton, New York, 1946.

selected with attention to the particular interest of each one in a definite topic. Consequently, a very personal attitude tinctures most of the papers in this collection. Almost half of the text is devoted to recent endocrine research, the interrelationship of the various glands, diagnostic methods of functional abnormalities, and the therapy of such disorders. The remaining text discusses the sterility problem, infections, benign and malignant growths, technique of gynecic surgery, and pre- and postoperative care.

The first section on growth and physiology brings out the basis of the physiology of normal and abnormal menstruation, the menopause, blood changes, and the Rh factor in gynecology. Markee gives an excellent discussion on the morphological and endocrine basis for menstrual bleeding. Engle concludes that the excretion of gonadotropins is not related to symptoms of the menopause, but that both are controlled by estrogen replacement. Diamond points out the double risk of the gynecologic patient of sensitization to blood factors. In the section on diagnostic methods, Benedict describes and evaluates the more commonly used assays for testing the status of the endocrine glands. Burch and Phelps regard biopsy method as giving most conclusive evidence concerning occurrence of ovulation. Rakoff discusses the importance and technique of vaginal cytology in ovarian function, while Fremont-Smith and Graham feel the vaginal smear in diagnosis of cancer is an accurate, easier, and earlier method than the older techniques.

In the section on functional disorders, Sturgis offers a new classification of the amenorrheas, which Stein properly stresses as a symptom and not a disease. Hamblen gives a fine and practical presentation on excessive uterine bleeding, while Deutsch writes concisely on the important psychiatric component in gynecology.

The interrelationship of endocrine glands is portrayed in seven notable papers. Nathanson, in discussing hormones in relation to tumors, feels that hormones in themselves are not carcinogenic, but that as a result of excessive stimulation or atypical metabolism of the hormones the tissues of a susceptible person may be conditioned to the action of a carcinogenic agent. Davis regards gonadotropin therapy in ovarian failure as offering little to the patient. Reifenstein stresses the necessity of considering the function of the adrenal cortex and the anterior pituitary in all disorders of the ovary.

There is frequent overlapping of discussion in this book, not necessarily of a contradictory character, but rather of a correlation of different aspects of the same basic question, as for instance this presentation by Reifenstein, the discussion by Pratt on masculinization, virilism and hirsutism, and the section by Dokerty on Functioning Ovarian Neoplasms. In the opinion of the reviewer, this adds to the value of the book. Salmon, after a thorough analysis of androgen therapy in gynecology, is tempted to hypothesize the participation of the endogenous androgens in the sex hormone physiology of the human female. He concludes in the end that the *raison d'etre* of androgen therapy stems from its clinical effectiveness.

There is ample discussion by able authors of the various phases of sterility, reproductive infections, and benign growths. Malignancy of the various pelvic areas, always a major problem in gynecologic practice, is considered in a series of twelve excellent papers in which the status and technique of radium and x-ray therapy are set forth, as well as the surgery which may be used. Dresser ably discusses supervoltage x-ray treatment. The senior editor contributes an outstanding discussion on the radical surgical approach to carcinoma of the cervix. Morton says his personal feeling is that pelvic lymphadenectomy should be regarded as experimental only, at the present time it has no established place in the treatment of cervical cancer. In contrast, Nathanson feels that iliac lymphadenectomy should be carried out on a large series of cases to evaluate the effect of radiation on metastatic nodes, the incidence of nodal involvement, and its efficacy as a curative procedure.

Eleven articles discuss changes recently proposed in operative technique. Masson describes the technique and results in his total abdominal hysterectomy. The editors have contributed on enterocele and on tubal sterilization. Aldridge describes his operation for stress incontinence in urine. These descriptions and discussions of the operative techniques favored in the different clinics represented are a valuable part of the book. The final section on preoperative and postoperative care is in reality a discussion of chemotherapy, the use

of antibiotics, anesthesia, an excellent paper on venous thrombosis and pulmonary embolism by Linton, in which he states bilateral interruption of the superficial femoral veins is a justifiable procedure to carry out on patients over 50 years of age subjected to major abdominal or pelvic operations, especially for malignancy. Horrax cogently discusses the neurosurgical methods for palliation of pain due to inoperable pelvic malignancy.

The book is a valuable contribution to gynecologic literature as it offers definite personal opinions on almost every phase of the specialty by men eminently qualified to discuss the research of recent years, the clinical application of the findings; particularly it gives an extended presentation of the cancer problem, its diagnosis, and present-day therapy.

PHILIP F. WILLIAMS.

One of the landmarks in my student studies occurred in 1898 when I first came across Winter's **Gynecological Diagnosis** in which the clinical part was written by Winter; the gynecologic histology, then in its infancy, by Carl Ruge. Since then the number of gynecologic diagnoses have increased and appeared in various languages, but none, in my opinion, have ever approached Winter's interest, vivacity, and general understanding. Neuweiler has added a **Gynecological Diagnosis for Physicians and Students**[3] to the long list of predecessors. It is really the first one appearing in the German language since the onset of the World War. Its interest is mainly clinical, although all of the newer methods of diagnosis are considered. Wisely, he has not attempted to enter into the minutiae of bacteriological and serological methods of diagnostic measures other than to mention them. A great deal of emphasis is placed on visualization of the uterus and tubes, apparently only with lipiodol. Many x-ray pictures are contained in the text. He considers this type of investigation as nonambulatory. In insufflation, he recommends the Sellheim method of injecting air by means of a syringe, the sole control being a manometer, although the Rubin apparatus is both pictured and discussed. I am, therefore, not surprised that he says that from a diagnostic viewpoint, insufflation is often uncertain and that in at least 18 per cent of so-called "closed tubes" conception occurs. To my astonishment, laminaria are still recommended for dilatation preceding curettage. The content of this volume is a carefully planned description of practically all of the conditions met with in gynecology. Various methods of investigation are detailed, including history taking, examinations, instrumentarium, curettage, obtaining of secretions, and the various special investigative methods of which some have already been mentioned. The author then takes up the various areas of the genital tract in succession. The volume is profusely and adequately illustrated. There are some very beautifully colored plates. On the whole, the author has kept in view the needs of the practitioner, although rarer conditions are likewise adequately described. A very detailed and good description of endometriosis is given. Leucorrhea, sterility, and backache are concluding chapters. The volume is very worth while. If there were not already so many "gynecological diagnoses" in the English language the advisability of translation might arise, particularly as the high price of bookmaking in this country precludes the lavish use of colored illustrations.

R. T. FRANK.

The second edition of Novak's **Gynecological and Obstetrical Pathology**[4] appears after an interval of nine years. The author has the knack of a top rank journalist in

[3] **Lehrbuch der Gynäkologischen Diagnostik für Ärzte und Studierende.** von Dr. W. Neuweiler, a.o. Professor für Geburtshilfe und Gynäkologie an der Universität Bern. 474 pages. Hans Huber, Bern. 1946.

[4] **Gynecological and Obstetrical Pathology.** With Clinical and Endocrine Relations. By Emil Novak, A.B., M.D., D.Sc. (Hon. Dublin) F.A.C.S. Associate in Gynecology, The Johns Hopkins Medical School; Gynecologist, Bon Secours and St. Agnes Hospitals, Baltimore; Fellow, American Gynecological Society, American Association of Obstetricians, Gynecologists and Abdominal Surgeons and Southern Surgical Association; Honorary Fellow, Société Française de Gynecologie; The Royal Institute of Medicine, Budapest; Sociedad d'Obstetricia et Ginecologia de Buenos Aires; Central Association of Obstetricians and Gynecologists; Texas State Association of Obstetricans and Gynecologists; Past Chairman, Section of Gynecology and Obstetrics, American Medical Association. Second Edition. With 542 illustrations, 15 in color. 570 pages. W. B. Saunders Company, Philadelphia. 1947.

presenting facts in a striking fashion, and the courge to oversimplify in the interest of clear teaching. This enables him, for example, to describe the endocrinology of the menstrual cycle and of pregnancy in a mere eight pages of text.

The new edition contains over 100 new illustrations, a number of which are in colors. Particularly the number of gross illustrations has been increased. The very numerous microscopic illustrations are very excellent, and most illustrative of the text. To comment on only one or two subjects in the contents, although he states that only 30 cases of sarcoma of the vulva are reported, this, in my opinion, gives an impression that the condition is very rare. In my own experience, I have encountered several and never have considered them of sufficient importance to burden the literature with them. Again, in describing senile vaginitis, the bleeding not infrequently is due to the rupture of synechiae, either by the trauma of coitus or even coughing. This deserves mention.

The author's very conservative attitude in doubtful lesions of the cervix, particularly in young women, is to be highly commended, because it contracts so strikingly with the hysterical attitude now current. The book is sufficiently detailed to be of great value to the specialist and the pathologist, and yet so simply and interestingly written that it has a full appeal to the student and the practitioner.

R. T. FRANK.

The second edition of Schauffler's **Pediatric Gynecology**[5] has appeared after an interval of five years. It has been rewritten in parts and revised up to date. This was particularly necessary, because the introduction not only of sulfonamides but also of penicillin has altered the treatment of gynecologic infections in children just as much as it has in adults. The discussion on masturbation is very excellent. It individualizes, neither overemphasizing the "evil" as did the old school, nor quite as condoning as the more advanced psychoanalyst. Schauffler trusts more in change in environment, attitude, etc., than in coercion or encouragement. Although he describes circumcision in the infantile female, I personally have never had to resort to this operation. The chapter on abdominal malignancies could be improved by a little more method and orderliness. In my own experience true precocious menstruation is more frequent than the author apparently has encountered. In the excellent chapter on urology, prolapse of the ureter through the urethra is not even mentioned. While this is a rare condition, the importance of recognizing it is great because I have seen death following ill-advised amputation of the protruding edematous ureter. There is also a chapter on proctology. Of importance are the chapters on social service as well as the medical legal aspects applied to sex deviations in female children. The social service aspects are in collaboration with Mary L. Eggleston, those on medical legal aspects with Dan H. Northup and Stuart R. Simmel. All in all, this book is very useful indeed, particularly to the gynecologist who only occasionally sees children and adolescents.

R. T. FRANK.

Obstetrics

This book, **Postgraduate Obstetrics,**[6] by William F. Mengert, is intended for the physician in the average community who does obstetrics in a general practice. The frequency of a condition or complication, and its capacity for casualty, has been the determining factor in the length of its quite personal and fully explanatory discussion.

The diagnostic errors in pregnancy and in its differential diagnosis are emphasized. Prenatal care is regarded as consisting of observation, detection, and control, and it is noted that the best available prenatal care can be completely vitiated without the proper

[5]**Pediatric Gynecology.** By Goodrich C. Schauffler, A.B., M.D. Assistant Clinical Professor of Obstetrics and Gynecology, University of Oregon Medical School; Visiting Gynecological Surgeon and Obstetrician, Multnomah Hospital, Portland, Oregon; Consultant and Teaching Gynecologist-Obstetrician to China Program, UNRRA. Second Edition. 380 pages. The Year Book Publishers, Inc., Chicago. 1947.

[6]**Postgraduate Obstetrics.** By William F. Mengert, M.D., Professor and Chairman, Department of Obstetrics and Gynecology, Southwestern Medical College. Chairman Obstetrics and Gynecology, Parkland Hospital, Dallas, Texas. 373 pages with 123 illustrations, Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York, London, 1947.

conduct of labor. Mengert cautions against introduction of infection in the last month, and suggests that therapy of trichomonas should be discontinued during this period. Postpartum sterilization is advocated in all patients with proved hypertensive disease.

There is an extended discussion of the abortion problem. An excellent outline of procedure is offered for patients suspected of having placenta previa. Mengert states that 75 per cent of all cases of placenta previa can be treated by rupture of the membranes with or without scalp traction (Willet's forceps) with minimal danger to the mother and less than 20 per cent fetal mortality rate. Organotherapy in obstetrics is an excellent section. The clinical methods of estimating pelvic capacity are emphasized in discussing cephalopelvic disproportion, and Mengert states that the prognosis of the outcome of labor is the function of the accoucheur and not of the radiologist.

In the conduct of labor, Mengert explains clearly the mechanism of separation and expulsion, and stresses noninterference. In the outline for medical induction, the dosage of pituitary extract exceeds that given by other authors. Later, in discussing prolonged labor, extreme caution is recommended in the use of the drug in inertia uteri. An excellent review of methods for relief of pain in labor ends with a section on the deleterious effects of analgesic and anesthetic drugs, a timely warning for the community obstetrician. The incompatibility of cyclopropane and pituitary extract and the possibility of the combination producing shock are noted. In discussing postpartum hemorrhage, the use of a hot intrauterine douche is recommended as a uterine stimulant. The repair of lacerations, especially complete tears, is well described, but it would appear that too many sutures are used, or at least indicated in the illustration, Fig. 46.

The author states clearly the requisites, the indications, and the technique of forceps operations. He regards the originally described application of Kielland forceps as the ideal method of dealing with arrest of labor in occiput transverse or obliquely posterior positions. This technique may be difficult for the family physician for whom the book is intended. The axioms on cesarean should sharpen attention, ante partum, to the possible necessity of this procedure; the section on "Lack of Indication" raises points worthy of scrutiny in a personal or group series. In this connection the author comments later, in discussing the elderly primigravida, that the importance of the child's life must not be exaggerated beyond the bounds of reason. Version and extraction is regarded as not an elective operation. The practical techniques suggested in the sections on postpartum care and care of the newborn and premature are used on the author's service.

The clinical types and newer therapies of puerperal infection are discussed at length. Droplet contamination is stressed. There are excellent chapters on follow-up examinations, miscellaneous complications of the puerperium, sterility, the emotional stresses of pregnancy, laboratory techniques, and the obstetric and gynecologic nursing techniques of the Parkland Hospital, Dallas. The book is cover full of concisely expressed information and clearly stated directions; as a practical guide for the family physician in his frequent obstetrical problems it could hardly be excelled.

PHILIP F. WILLIAMS.

In this book, **The Essentials of Obstetrics and Gynecology,**[7] the authors, Scott and Van Wyck, have recognized the growing integration of the two subjects in research and clinical practice, and present the basic teaching in them given at the University of Toronto. The text is limited to fundamental principles, but covers practically every topic of value in the two subjects.

The discussions on anatomy and physiology have been skillfully handled to open either division, while the physiology of pregnancy, especially the section on metabolism, is complete as well as concise. The authors add a new phrase "control of the patient,"

[7]**The Essentials of Obstetrics and Gynecology,** by William Albert Scott, B.A., M.B., F.R.C.S. (Can.), F.R.C.O.G. (Eng.), Professor of Obstetrics and Gynecology, University of Toronto, and H. Brookfield Van Wyck, B.A., M.B., F.R.C.S., (Can.), F.R.C.O.G. (Eng.), Assistant Professor of Obstetrics and Gynecology, University of Toronto, 381 pages. With 91 illustrations, 13 in color. Lea & Febiger, Philadelphia. 1946.

in a section which gives directions for her care in a quite specific manner. There is a detailed description of home delivery service, a point well taken in these days of crowded maternity hospitals. Early ambulation is favored after labor.

Contraception forms a separate chapter, and while the authors stress the avoidance of pregnancy in many conditions, they are not equally emphatic as to the need for simultaneous sterilization in connection with therapeutic abortion. The use of the Mann forceps, an instrument with a universal joint between the blades and the shank, regarded as advantageous in persistent occiput posterior positions, is described in an excellent discussion of operative obstetrics.

The second phase of this dual presentation, gynecology is equally well handled, especially the relationship of functional disorders, and physical abnormalities of the reproductive system. The illustrations in this section are beautifully done. Pathology is treated regionally. There is an excellent recapitulation in a separate chapter of previous discussions of abnormal uterovaginal bleeding. The authors go lightly in recommending endocrine therapy. Operative procedures are described briefly, but are well illustrated.

This precise and logical manner of offering the fundamentals and modern practice of both subjects leaves little to be desired in such a combined textbook for either student or general practitioner.

PHILIP F. WILLIAMS.

Doctor Murphy offers in **Uterine Contractility in Pregnancy**[3] the methods and results of a study with a Lorand tocograph, and the conclusions which he has deduced. Some 3,200 individual records of uterine contractions form the basis of the studies. The apparatus, which apparently is easily used, records fetal movements as well as contraction of the uterus. In the former response the apparatus may be useful in helping to diagnose death of the fetus. The tocograph measures primarily the hardness of the uterine muscle, and the tracings exhibit both tone of the muscle and contractions. The author notes that uterine contractility has its greatest increase about the thirty-second week of pregnancy, and the time that this phenomenon appears prior to the thirty-second week indicates significant shorter labors. A single tracing, however, is not sufficient basis for prediction of the type of labor to be expected. An increase in the uterine tone is usually observed in primiparas in the sixth month, but usually later in multiparas; the degree of tone, however, is not of significant value in predicting the onset or character of a labor.

Pregnancy contractions have been studied with regard to the effect of pituitary extract and estrogenic substances. In regard to pituitary extract, Murphy feels that a tetanic type of response to the drug occurs when the dose of the drug was large and when uterine tension was high, and concludes from his observations that the amount of pituitary extract for optimum results in the induction of labor or for a stimulating effect in labor should be extremely small, and only sufficient to produce a uterine reaction. He suggests that the optimum dose in labor should be less than one minim. The effect of estrogens on contractility was variable, but no reaction occurs prior to the twenty-ninth week. Morphine appears to influence the intermittent contractions to a greater degree than the tension of the uterus, and would seem to rest the uterus during labor by reducing the frequency of the contractions.

As to inertia uteri, the problem which originated the study, Murphy found that the tocograph will early distinguish the type of inertia present, and is of value in selecting patients suitable for stimulus by oxytocics. Similarly, repeated tracings during a prolonged labor will register the first appearance of secondary inertia.

---

[3]**Uterine Contractility in Pregnancy**, A Study of the Contractions of Pregnancy and Labor under Normal and Experimental Conditions. By Douglas P. Murphy, M.D., F.A.C.S., Assistant Professor of Obstetrics and Gynecology and Research Associate in the Gynecean Hospital Institute of Gynecologic Research, University of Pennsylvania. 130 pages. With 64 illustrations. J. B. Lippincott Company, Philadelphia. 1947.

This is a very fine study of the physiology of the pregnant and the parturient uterus, and its response to some commonly used agents. There is no doubt but that the clinical application of the method and a correct interpretation of repeated graphs will be of significant value to the obstetrician in atypical labors.

PHILIP F. WILLIAMS.

The Problem of Fertility, edited by Earl T. Engle,[9] represents the proceedings of the Conference on Fertility, held under the auspices of the National Committee on Maternal Health, in 1946, and presents sixteen papers on the fundamental biological factors concerned in the physiology of reproduction. Ten of these papers recount the application of such basic principles in animal husbandry. The purpose of this recent conference was to reveal the present status of the investigations of reproduction in domestic animals to a large group of clinicians interested especially in the problem of human fertility. While the papers are indeed excellent, the physician interested in human sterility will gain much from the well-edited discussions which followed the reading of each paper.

Of particular note among these proceedings was the evaluation of the fertility of ova produced by use of pituitary gonadotrophins; the methods used in horse breeding to insure ovulation after insemination; and the fertilizability of the equine sperm. Corner presents a fine article on the ovary at the time of ovulation, and the succeeding discussion brought out the presently understood physiology of the granulosa and the theca. The debate following Coles' article on hormonal control of ovulation showed a variance of opinion in the Conference. There is ample consideration, begun by Pommerenke, of the cervix, its mucus, the content of the mucus, and its relationship to infertility in the human being. Four excellent papers brought out recent vital significant facts regarding bovine, human, and rabbit spermatozoa. Artificial insemination was fully discussed both from the standpoint of animal husbandry and the human problem. Simmons' paper on the cervix uteri in infertile matings summarizes a most important phase of the question, and he proposed what he terms "a normal post-coital test."

This presentation of what has been accomplished by animal breeders and the discussion how the advances may be made useful in the human field make the report of the Conference one of significant value in the study of infertility.

PHILIP F. WILLIAMS.

Surgery in Obstetrics by Keller and Ginglinger[10] describes the practices of the Strasbourg Faculty of Medicine. Two introductory chapters deal with conditions met with before conception, particularly malformation of the genital tract. For absence of the vagina, the Baldwin-Mori operation is still discussed and, in fact, is the only operation in the book which is illustrated. The newer skin plastic methods are described. No mention of nonoperative formation of a vagina can be found. Another chapter is devoted to the non-infectious sequelae of labor. In hematocolpo-metro-hematosalpinx, laparotomy is always insisted upon. The surgery for acquired sterility is mentioned, including salpingolysis, implantation of the tube and ovario-uterine implantation. The authors claim that the world literature shows 5 per cent of successes. Ectopic pregnancy is likewise discussed; also the complications encountered in pregnancy and delivery after the uterus has been subjected to various methods of fixation. In the treatment of therapeutic abortion the method of Boero is advocated after the third month. This consists in the injection of 40 per cent formalin into the fetal sac through an intra-abdominal puncture (!). The authors have not yet had an opportunity to test the efficacy of penicillin. All the various difficulties encountered in pregnancy and labor are described with considerable minuteness.

---

[9]**The Problem of Fertility,** Proceedings of the Conference on Fertility held under the Auspices of the National Committee on Maternal Health, Edited by Earl T. Engle. 250 pages. With illustrations. Princeton University Press, Princeton, New Jersey. 1946.

[10]**La Chirurgie en Obstétrique.** By R. Keller, Professeur de Clinique d'Obstétrique et de Gynécologie, et A. Ginglinger, Délégué dans les fonctions d'Agrégé d'Obstétrique et de Gynécologie a la Faculte de Medecine de Strasbourg. Preface du Pr Reeb. 232 pages. Masson et Cie, Paris, VIe, France. 1946.

In my opinion, the title "Surgery in Obstetrics" is somewhat misleading, as no attempt is made in describing or illustrating the technical surgical procedures.

The book is illustrated by one of the authors, Keller. He has devised a very simple, striking technique of showing all the cavities in deep black and indicating the parietal walls or structures by lighter line drawing. The book is interesting to read, but offers very little new to the American reader.

R. T. FRANK.

Debiasi, who is Director of Obstetrics at the school of Udine, has written on the **Anemia of Pregnancy**[11] covering the cases observed in the clinic of Catania and Sassari. He mentions that no recent Italian studies exist, the last one dating to 1903. This is a large 400-page monograph, on rather poor paper, which is a pity because the blood pictures do not show up as well as they might, although they are sufficiently characteristic to be of value. The anemias dealt with are acute posthemorrhagic, chronic hemorrhagic, the hyperchromic, pernicious, pseudopernicious, and macrocytic. From another aspect, there has been a classification into symptomless oligocytemia, the cidropenic, megaloblastic and aplastic varieties. There are a large number of thoroughly studied cases which are described in extenso. The book should prove of value to both gynecologists and hematologists.

R. T. FRANK.

The ninth edition of DeLee's **Principles and Practice of Obstetrics**[12] represents an extensive revision by J. P. Greenhill. Although much new material has been added, this edition, aided by a new double column format, is 100 pages shorter than the previous one.

Among the new chapters is one on "Minor Disturbances of Pregnancy" treating the items which cause most telephone calls and much of the consultation conversations. In another new section the problem and diagnosis of Postmaturity and Missed Labor with death of the fetus are given. Greenhill advocates induction if one is sure of postmaturity or fetal death. Davidsohn wrote the new chapter on Erythroblastosis Fetalis. It is an extended discussion, but does not mention titer determinations in the mother, or prophylactic cesarean or early induction to prevent fetal damage. Directions which may increase fetal salvage are given in a new chapter on Care of the Premature. A section is added on Circumcision, but the presently popular clamp method is omitted.

In addition to these new chapters many changes have been made in other sections. This is notably so in the discussion of anesthesia and pain relief. Greenhill apparently prefers local infiltration where it is possible, often combining it with pentothal sodium intravenously, and he states he has used cyclopropane extensively and satisfactorily. Spinal and caudal anesthesias are not regarded favorably.

Induction of abortion is recommended in pregnant women who have had German measles in the first three months on account of the danger of congenital abnormalities. There is a full consideration of the use of penicillin in various complicating lesions and diseases.

The section on obstetric endocrinology sums up the physiology of the glands, indications for, and dosages of the various hormones which have been found helpful in obstetric practice, as well as a discussion of the various animal tests for pregnancy and chorionepithelioma.

---

[11]**Anemie E Gravidanza.** By Prof. Ettore Debiasi, Direttore inc. della Scuola di Ostetricia di Udine. Con Prefazione del Prof. E. Maurizio, Direttore della Clinica Ostetrica e Ginecological di Catania. 400 pages. Dr. Francesco Montuoro, Editore, Milano, Venezia. 1946.

[12]**Principles and Practice of Obstetrics,** by Joseph B. DeLee, M.D., Late Professor of Obstetrics and Gynecology, the University of Chicago; Consultant in Obstetrics, the Chicago Lying-in Hospital and Dispensary, and J. P. Greenhill, M.D., Attending Obstetrician and Gynecologist, the Michael Reese Hospital; Professor of Gynecology, Cook County Graduate School of Medicine. Ninth Edition. 969 pages. With 1,108 illustrations, 211 in color. W. B. Saunders Company, Philadelphia and London. 1947.

The illustrations in this edition have been increased to 1,108, of which 211 are in color. Many stages of the mechanism and management of labor are illustrated by selected strips from DeLee's motion picture films. Some of the new color plates are beautiful reproductions of obstetric anatomy and pathology. This edition fully maintains the high position of the book as a modern and complete exposition of obstetrics in every particular.

PHILIP F. WILLIAMS.

Obstetrical Practice by Beck[13] appears in the fourth edition within a period of twelve years. The excellence of the author's presentation of his teaching in this clinical field has made the text a standard in obstetrical literature. Among the major changes in this edition are the sections on implantation and placentation, the application of penicillin to obstetric problems, and there has been added a very full discussion of amnesia, analgesia, and anesthesia.

In the discussion of implantation and placentation, Beck has modified the chapters to accord with the recent observations of Heuser and Streeter on the blastocyst stage, and the views of these authors, and those of Hertig and Rock and Brewer on the lacunar stage, and the method of implantation as shown in the very early embryos which these men have been able to recover from the human uterus.

In the history outline and the outline of physical examination Beck omits obtaining a history of previous transfusions and of Rh factor determination, although the latter is discussed briefly in the text in changes in the maternal organism, the management of pregnancy, and the etiology of abortion. Any discussion of titer determinations and treatment based on them is not given. There is an excellent discussion of penicillin in maternal infection in the preventation of congenital syphilis. Penicillin is not, however, mentioned in the treatment of gonorrhea in the pregnant woman.

In the new and excellent chapter on the relief of pain in labor practically all the recently proposed methods are discussed as to the advantages and disadvantages. Beck states that local anesthesia combined with demerol and scopolamine is the simplest, safest, and the most satisfactory method for the average woman in the hands of the average practitioner. As to continuous caudal anesthesia he states, "The technique is difficult to master, and the margin of safety for the mother is so narrow that the constant supervision by one capable of recognizing and treating the first evidences of an untoward reaction is imperative." The same words of caution are also applied to the use of spinal anesthesia in obstetrics, while the dangers associated with chloroform, ethylene, and cyclopropane are stressed.

One may again recommend the comprehensive diagrams of the mechanisms of labor, and the profuseness of the serial illustrations in the section on operative obstetrics.

PHILIP F. WILLIAMS.

Greenhill's (1946) **Year Book of Obstetrics and Gynecology**[14] appears as regularly as the first signs of spring. It proves a handy reference source to look up articles and an even more useful guide for quickly envisaging any new developments in these two subjects. The short but pungent editorial notes are impartial, illuminating, and to the point. The liberal use of illustrations adds to the value of this indispensable guide.

R. T. FRANK.

---

[13]**Obstetrical Practice**, by Alfred C. Beck, M.D., Professor of Obstetrics and Gynecology, Long Island College of Medicine; Obstetrician and Gynecologist-in-Chief, Long Island College Hospital, Brooklyn. Fourth Edition. 921 pages. With 1,068 illustrations. The Williams & Wilkins Company, Baltimore. 1947.

[14]**The 1946 Year Book of Obstetrics and Gynecology.** Edited by J. P. Greenhill, B.S., M.D., F.A.C.S., Professor of Gynecology, Cook County Graduate School of Medicine; Chairman, Department of Gynecology, Cook County Hospital; Attending Obstetrician and Gynecologist, Michael Reese Hospital; Associate Staff, Chicago Lying-In Hospital; Author of Office Gynecology and Obstetrics in General Practice; Co-author of the DeLee-Greenhill Principles and Practice of Obstetrics. 655 pages. The Year Book Publishers, Inc., Chicago. 1947.

De Moraes' **Propedêutica Obstétrica**[15] appears in its sixth edition since 1924. The author, who is very prolific, has contributed to the obstetric and gynecologic literature since 1915. The present edition has been brought fully up to date and will continue to serve as a good introduction to the study of obstetrics. The topics of modern hormone studies have been brought up to date. There is a very full description of pregnancy tests. I venture to suggest that it would now suffice to mention the Abderhalden pregnancy test merely for its historical interest. The chapter on toxemias of pregnancy deserves special mention because of the thorough discussion. There is innumerable mention of quoted authorities without a single bibliographic reference.

R. T. FRANK.

The **Transactions of the Rioplata Obstetrical and Gynecological Society** from the year 1946[16] contains a large number of articles on very diversified subjects in both obstetrics and gynecology. To give an idea of its heterogeneous contents, there are articles on dermatological lesions in pregnancy, a number of papers dealing with radiotherapy (in both malignant and nonmalignant conditions); some papers on technical obstetric procedures such as forceps, cesarean section, continuous epidural anesthesia, and related gynecologic subjects such as arterial hypertension. Many gynecologic technical papers are included. From the standpoint of completeness of the literature, the transactions are worth considering.

R. T. FRANK.

Even if belatedly, we welcome (published in 1943) the first book received from Italy since the war. Merlino's monograph on **Abruptio Placentae,**[17] after discussing what is known on the subject in detail, presents 110 cases treated at the University of Naples. The incidence is unduly high, as only 7,218 pregnant women were delivered during this period, 1937 to 1940.

The world's statistics show such a tremendous variation in results—maternal mortality between 94 and 2.9 per cent, fetal mortality between 94 and 2.9 per cent—that worth-while comparisons are out of the question. Of the 110 cases, exactly half delivered spontaneously; 33 were delivered per vaginam; 23 by abdominal section. This large and well-presented material deserves careful study. The many "errata" found in this otherwise faultlessly produced monograph doubtless are due to the disturbed conditions in 1943.

R. T. FRANK.

Dr. Montagu in this small monograph **Adolescent Sterility**[18] discusses the time which elapses between the appearance of the first menstruation and the ability to conceive and carry a fetus to term.

It is evident from this thoroughly documented study that such a definite time interval does exist, both in the human being and the experimental and domestic animals, the lower mammals, the cow, rhesus monkey, and chimpanzee. In the animal group the interval dates from the first oestrus for a period apparently specific for each animal. After studying the different

---

[15] **Propedêutica Obstétrica.** By Arnaldo de Moraes, Professor Catedrático de Clínica Ginecológica da Faculdade Nacional de Medicina da Universidade do Brasil. 6.a Edição. Revista E Atualizadas Pelo Autor. Com 512 páginas e 168 gravuras, das quais duas tricromias. Ilustrações adaptadas e originais de L. G. Loureiro. 495 pages. Livraria Francisco Alves, Rio de Janeiro, Brazil. 1946.

[16] **VI Jornadas Rioplatenses de Obstetrician y Ginecología.** Actas Y. Trabajos. Montevideo, 21-22 y 23 de Marzo de 1946. Sociedad Ginécotocologica del Uruguay. 449 pages. Comision Organizadora. Montevideo. "Rosgal," de Hilario Rosillo, Montevideo, Uruguay. 1946.

[17] **Il Distacco Intempestivo di Placenta Normalmente Inserta** (con 40 figure nel testo). Antonio Merlino, Aiuto e Docente di Clinica Ostetrica e Ginecologica nella R. Università di Napoli. Prefazione del Prof. Salvatore Cappellani. 235 pages. Rosenberg & Sellier, Torino, Italy. 1943-XXI.

[18] **Adolescent Sterility,** A study in the Comparative Physiology of the Infecundity of the Adolescent Organism in Mammals and Man, by M. F. Ashley Montagu, Associate Professor of Anatomy, Hahnemann Medical College, Visiting Lecturer, Department of Sociology, Harvard University. 141 pages. Charles C Thomas, Springfield, Illinois. 1946.

time intervals in various human racial groups, the author concludes that environmental and nutritional factors may have a bearing. From a biological standpoint, he regards this sterile period as one of gradual maturation of the endocrine glands until the effect of their secretions has finally brought the reproductive tract into full maturity—nubility.

PHILIP F. WILLIAMS.

Di Paola was commissioned by the Sixth Congress of the Argentine Society of Obstetrics and Gynecology to treat the subject of the **Physiology of Adolescence.**[19] This period approximately covers the twelfth to eighteenth year. The morphology including the somatic and sexual changes, the endocrine aspects and finally the methods of study and investigation are described. There are 27 illustrations.

R. T. FRANK.

Eastman's **Expectant Motherhood**[20] has gone through fifteen reprintings since the appearance of the first edition. There can be little doubt that thousands of women have benefited by reading the author's "whys and wherefores" on prenatal care and labor, and that busy office hours of many obstetricians have been helped by the efficient and accepted teachings which the book sets forth. In the new second edition is an ample discussion of nutrition and diet, an understanding of which by the patient will do much to help obstetricians control the frequent too rapid gain in weight. Foods have been divided into seven groups with their values and explanations of their necessity and the proper amount. These concise instructions are a valuable addition to the book. Chapters on clothing and preparation for the baby are excellent. The chapter on painless childbirth is a rational exposition of how pain in labor can be relieved and it should do much to reduce the recurring waves of enthusiasm, by lay publicity, for each new type of relief which may be proposed.

There is probably no better book available to recommend to obstetric patients for necessary information in such a simple and practical form.

PHILIP F. WILLIAMS.

This charming and delightful book **Modeling for Motherhood**[21] is addressed to all pregnant women, for all of them, or nearly all, are worried about their figure and appearance during and after the event. They need advice and guidance not only in the maintenance of proper and adequate diet, but how to develop their muscles for the coming labor. With proper prenatal care, a woman can carry out her most important function in life without ending up as a "bedraggled wreck." After sound directions about choosing doctors, nurses, hospitals, etc., a great deal of attention is accorded to posture, to exercise, to a manner of living, all of which will contribute to make this period of life a happy rather than a mournful one. And the text is written in an amusing fashion and gaily illustrated. It is free from the didactic and academic style of many of the books on "Motherhood" produced by doctors, although the warnings about possible troubles are not omitted. The book might well be in the possession of every prospective mother and also deserves the attention of physicians.

GEO. W. KOSMAK.

---

[19]Tema Oficial **Fisiologia De La Adolescencia.** Relato Del Dr. Guillermo Di Paola. Sexto Congreso Argentino De Obstetricia Y Ginecologia, Buenos Aires, 20 A1 26 de Octubre de 1946. 95 pages. Secretaria Del Congreso, Buenos Aires.

[20]**Expectant Motherhood,** by Nicholson J. Eastman, M.D., Professor of Obstetrics in Johns Hopkins University; and Obstetrician-in-Chief to the Johns Hopkins Hospital. Second Edition, revised. 193 pages. With 13 illustrations. Little, Brown and Company, Boston. 1947.

[21]**Modeling for Motherhood.** By Doris Hale Heinz and Katherine Smith Bolt. Illustrated by Doris Hale Heintz, with foreword by Frederic M. Loomis, M.D. John Wiley and Sons, Inc., New York. 1947. Price $2.

Endocrinology

"Ovarian Tumors" in two large volumes has appeared as an independent unit (Vol. VII) of Selye's **Encyclopedia of Endocrinology.**[22] The concept of one man undertaking such a gigantic task is somewhat disconcerting, but the author has made a brave beginning. The large volume of 427 pages containing 15,000 references on ovarian tumors, alphabetically arranged according to author, but readily referred to by a simple system, contains references from antiquity to recent years. It covers the literature of every country and every language, but in its completeness does not reach the precision of an *Index Medicus*, as I convinced myself by a rather careful perusal of its pages. Moreover, one may well doubt the value of including 27 references to Atlee (1844-1882) or of I. B. Brown on "ovarian dropsy" 33 references (1840-1871); or the two full crowded columns of references to the "common ovarian cyst," some 320 in number, on page 101 of the text.

The second volume (Ovarian Tumors) is an ingeniously arranged loose-leaf cover containing 284 pages of text plus 60 pages of a "List of Periodicals" with 10 index tabs to facilitate ready reference. The closely printed two-column page really doubles the length of the text. In addition, there are 37 full-page plates averaging from 5 to 9 figures on each, many gross, more microscopic, some x-ray photographs, etc., faultlessly reproduced. The majority are from the author's large collection, though many are from other sources to whom due credit is given.

The text has been planned "to serve as a guide to, and a critical summary of, the relevant literature. . . ." The gynecologist and endocrinologist are the audience sought for. Selye presents eight classifications of ovarian tumors from the literature (Goodall, Conill, Schiller, Novak, Ten Teacher's, Miller, Geist, H. C. Taylor, Jr.) and then the one which he uses in his encyclopedia. This latter is in two columns—benign and malignant, and under each "potentially endocrine neoplasms" and "nonendocrine tumors." Of the potentially endocrine, there are no less than 17 categories.

The text is very systematically arranged, covering synonyms, reviews, definition, history, classification, pathologic anatomy, incidence, pathogenesis, clinical course, complications, diagnosis, prognosis, and therapy. A very worth-while addition under each variety of tumors is a short chapter showing its occurrence in animals, as, for example, "Ovarian Common Carcinomas in Animals." "Ovarian Teratoids in Animals." The avian equivalent of a dermoid, by the way, contains feathers instead of hair!

Endometriosis is included, as it may be considered a neoplasm. In a personal statistical analysis of 160,324 gynecologic patients, the author found that 4,503, or 2.8 per cent, showed ovarian tumors.

This immense accumulation of facts correlated, systematized, concentrated, and presented under the guidance of an exceptionally gifted and industrious scientist is a noteworthy accession to the literature of gynecology and endocrinology.

R. T. FRANK.

Claude Béclère publishes a large (371 pages) monograph on **Hormonal Diagnosis and Hormonal Therapy in Gynecology.**[23] The introduction is by Simonnet with whom Béclère has collaborated for years in both laboratory and clinical investigation.

To me, the attempt at innumerable subdivision based on clinical, bio-assay and other criteria has become more and more abhorrent. Realizing the extreme unreliability of various tests, the many incalculable factors, both local and general which enter the picture, I have

[22] **Encyclopedia of Endocrinology** by Hans Selye, M.D., Ph.D. (Prague). D.Sc. (McGill). F.R.S. (Canada). Professor and Director of The Institute of Experimental Medicine and Surgery, University of Montreal. Section IV, Ovary, Volume VII Bibl., Ovarian Tumors (Bibliography). 427 pages. Section IV, Ovary, Volume VII, Ovarian Tumors. 289 pages. Richardson, Bond and Wright, Montreal, Canada. 1946.

[23] **Diagnostic Hormonal et Traitements Hormonaux en Gynécologie.** Par Claude Béclère. Préface du Professeur H. Simonnet. 371 pages. Masson et Cie, Paris, VIe. 1946.

tried to simplify not complicate the analysis. However, this large, detailed study, based upon ample material will prove of interest to many enthusiastic therapeutists who treat their patients much more empirically than does the author.

After excluding organic lesions as surely as is possible, he subdivides the groups on a purely clinical basis—young virgins, young women, 40 years to the menopause, postmenopausal. The effect of therapy—estrogens, progesterones, and male sex hormones are used both in diagnosis and therapy.

R. T. FRANK.

Bishop[24] has written a short, 124-page monograph in small format, on practical endocrinology for the practitioner, of which 40 pages are an appendix showing the various preparations of "sex hormones," notwithstanding the fact that this book was written to tell the general practitioner "which hormones to use in treatment" and that the author appears to harbor a rather poor opinion as to the knowledge of the general practitioner. The book is clearly and well written. In addition to treatment, it takes up the various syndromes, such as amenorrhea of which one cause is ascribed to pituitary "shock," dysmenorrhea, infertility, and pregnancy. The pregnancy tests are taken up in considerable detail, as well as hormone assays which are at least referred to. For anyone desirous to brush up in complete knowledge, the book might be of service.

R. T. FRANK.

The second edition of Grollman's **Essentials of Endocrinology**[25] has appeared after an interval of six years. It has been brought fully up to date. This book contains an immense amount of fundamental information presented in a very readable and understandable fashion. The introduction to each gland, covering the anatomy, embryology, as well as physiology, is very soundly treated. The transition to the clinical facts thus being smoothed out, are understandable and clearly described. The division of the glands according to their location, that is in the cranial cavity, those of the branchiogenic origin, and those in the abdominal cavity, is a bit startling but nevertheless logical.

The hypophysis is very adequately dealt with. The author says that the clinical inadequacy of the anterior hypophyseal extracts must be faced and yet on page 94, he states, "the anterior pituitary extracts are indicated when there is evidence of hypophyseal cachexia," which shows how difficult it is to resist the pressure exerted by clinicians for some treatment of serious conditions. He states unequivocally that the concept of antagonist and synergist is no longer accepted in accounting for gonadotropic action. He likewise doubts greatly that thyrotoxicosis is due to hyperpituitary stimulation. In fact, throughout the book, he is very reserved in accepting exaggerated claims. His stand on Cushing's disease is that pituitary adenomas are rarely the cause. On the other hand, some cases may be actually due to hypothalamic disease. The author's "metabolic craniopathy" seems to be an "ominum gatherum" on a very weak foundation. Whether the purely embryologic basis for describing the thyroid, parathyroid, and thymus under the grouping of "branchiogenic" is justified should remain an open question.

It is hardly necessary in this second edition to take up each organ seriotim because he has done justice throughout and quite impartially. Some rather important conditions are treated in a very cursory fashion as, for instance, the three-fourth page discussion of dysmenorrhea and the coverage of sterility in a page and a half. There is a concluding

[24]**Gynaecological Endocrinology for the Practitioner.** By P. M. F. Bishop, D.M. (Oxon.). Lecturer in Applied Physiology, Guy's Hospital Medical School; Clinical Endocrinologist, Guy's Hospital; Endocrinologist to Chelsea Hospital for Women. 124 pages. Williams and Wilkins Company, Baltimore. 1946.

[25]**Essentials of Endocrinology.** By Arthur Grollman, Ph.D., M.D., F.A.C.P., Professor of Medicine and Chairman of the Department of Experimental Medicine, the Southwestern Medical College; Attending Physician and Consultant in Endocrinology, the Parkland Hospital, Dallas, Texas. Second Edition, Revised and Enlarged. 644 pages. With 132 illustrations. J. B. Lippincott Co., Philadelphia. 1947.

chapter on the hormones derived from nonendocrine organs, covering those of the gastrointestinal tract and the still supposititious cardiac, liver, renal, etc., ones.

The value of the chapter bibliographies is somewhat diminished by the author's fondness for singling out reviews and limiting his quotations rather strictly to all literature published during the last ten years. On the whole, this is a very satisfactory and sound presentation of the subject, showing that endocrinology is beginning to reach a more stable status.

R. T. FRANK.

Wallet[26] has spent four years in de Gennes' clinic in gathering evidence of hyperestrogenic secretion as well as of hyperluteinization. This elaborate monograph, which quotes 1,220 works from the world's literature, is based largely on endometrial histologic findings (biopsies).

The chemistry, physiologic effects, metabolism, etc., of estrogens is taken up in detail, as is the uterine and vaginal cycle, the role of the hypophysis, the interrelation of the glands. The blood and urine hormone assays are described in detail, but evidently were not employed in this research, which is mainly based on uterine biopsies obtained by the Novak apparatus. Based on these criteria, a very detailed symptomatology, which embraces all the known functional deviations as well as organic lesions such as fibroids and cancer, are viewed from this very onesided and artificial aspect.

R. T. FRANK.

In a more than 300 page monograph, Dr. Jules Samuels describes the **Hormone Maintenance of the Fetus.**[27] This same endocrinologist, in 1938, published a pregnancy test by means of spectroscopic examination of the blood, a test which was never regarded seriously by other investigators. I confess that I was unable to read this book with either care or interest, in spite of the fact that it has 544 references to the literature and covers pregnancy not only in the human being, but also in the mare, monkey, cow, rat, pig, and other mammals; likewise pregnancy reactions in human beings and animals. This monograph is supposed to be a part of an as yet uncompleted five volume endocrinology which deals especially with the dysfunction of the hypophysis, its diagnosis and therapy. The author considers the gonadotropic factor a cell activator and in cell division, an accelerator. The thyrotropic factor is an activator of the multiplication rate. He has made studies of the prepituitary and placenta in various animals. Fortunately, there is a summary at the end of the book in four different languages. To read even the English summary, which covers 18 pages, proves an arduous task and has in no way clarified my concepts of this rather involved question. Whether it will prove of any use to special investigators on the subject, I must leave to their own judgment.

R. T. FRANK.

Miscellaneous

Currents in Biochemical Research,[28] edited by David E. Green, is a most unusual and intriguing book. Under one cover, thirty-one well-known investigators have described "in as simple language as possible" the important developments in their own field. The scope is immense, covering pharmacology, chemotherapy, public health, genetics, photosynthesis, and agriculture, viewed from the organic analytical and physical chemistry angles. I do not say that every reader will study each article with equal care, but I cannot conceive of

[26] **L'Hyperfolliculinie. Étude Clinique, Anatomopathologique et Thérapeutique.** Par Max Wallet. Préface de L. De Gennes. 354 pages. Masson et Cie, Paris (VIe). 1946.

[27] **Die Hormonversorgung des Foetus.** von Dr. Jules Samuels, Chirurg Frauenarzt, Spezial Arzt für endogene Endokrinotherapie, Amsterdam. 320 pages. E. J. Brill, Leiden. 1947.

[28] **Currents in Biochemical Research.** Edited by David E. Green. Thirty-one essays charting the present course of Biochemical Research and considering the intimate relationship of biochemistry to medicine, agriculture and social problems. 486 pages. Interscience Publishers, Inc., New York. 1946.

any physician who will fail to find at least several essays which will prove of absorbing interest to him. Moreover, the authors have kept their promise in presenting their subject in a fashion understandable to the average physician.

Beadle of Stanford deals with "The Gene and Biochemistry." He emphasizes the similarity of genes and viruses. These basic functional units can be influenced (mutation) and can be used as "tools in determining the course of biosynthesis. . . ." "Viruses," by Stanley of the Rockefeller Institute, are submicroscopic entities which produce proliferative or degenerative changes in the cells they have invaded. These crystallizable nucleoproteins possess an "activity somewhat akin to that possessed by certain protein hormones and enzymes." Gaffron of the University of Chicago, describes "Photosynthesis and the Production of Organic Matter on Earth which makes possible the abundance of living things on the earth." The gap between the demand for and the supply of organic material is diminishing hourly, just as we are cutting down our forests three times as fast as they grow.

It is quite impossible to do justice to this book by even the briefest of reviews. If only I can whet the appetite of the reader sufficiently to make him take up this treat, he will continue of his own accord. The bacterial cell (Dubos); the nutrition and biochemistry of plants (Hoagland); the biological significance of vitamins (Elvehjem); some aspects of vitamin research (Folker); (the elucidation of their chemical constitution in ten years!); quantitative analysis in biochemistry (Van Slyke) (by the father of micromethods); hormones by Houssay; the steroid hormones (Pincus); plant hormones (Thimann); the chemical mechanism of nervous action (Nachmansohn); chemotherapy (Hotchkiss); some biochemical problems posed by a disease of muscle (Hoagland); social aspects of nutrition (Sebrell) are some of the subjects dealt with. The book contains a mine of information.

R. T. FRANK.

Penicillin in Syphilis, by J. E. Moore,[29] gives the present status of the agent and its clinical use. The sudden advent of penicillin in wartime brought about an organized investigation into its use in the problem of early syphilis in the armed forces. The result of its continued use in peacetime by a number of cooperating clinics has made available methods and results which are used basically in the text. The pharmacology of the agent, Chapter two, is a detailed account of the various techniques and potencies which have been employed, the nature of the effect on lesions of the various systems, and a discussion of the different species now produced.

Continuing chapters set forth with clarity the mechanism of action of penicillin, the manner in which its use for such infections as gonorrhea may mask the diagnosis of syphilis, and its employment in early, latent, and systemic lesions. The newness of the therapy and its apparently uncertain results in certain lesions have led to a note of caution in several places, as well as an emphasis on the responsibility of the physician who adopts this therapy to carefully follow up and repeatedly observe his patients after penicillin treatment.

The use of penicillin in treatment of the syphilitic pregnant woman forms an extended chapter. Among 76 women with manifest early syphilis so treated, only one infant developed congenital syphilis. In discussing this case, Moore suggests that a larger dose should have been given over a longer period, or that the patient should have been retreated because of lack of serologic response. The total dosage employed in the pregnant syphilitics has varied from 1.2 to 4.8 million units, in a period of eight to fifteen days. The statement appears that penicillin treatment on any stage of pregnancy is effective in preventing congenital syphilis, and again, that a negative serologic test in the mother at the time of delivery is not essential to the birth of a healthy infant. Abortions, reaction phenomena, actual and threatened, among the penicillin-treated syphilitic women do not equal the normally expected incidence of spontaneous abortions in nonsyphilitics. If a mother is apparently

[29] **Penicillin in Syphilis,** by Joseph Earle Moore, M.D., Associate Professor of Medicine and Adjunct Professor of Public Health Administration, The Johns Hopkins University; Physician-in-charge Syphilis Division of the Medical Clinic and Visiting Physician, The Johns Hopkins Hospital; Chairman, Syphilis Study Section, National Institute of Health, United States Public Health Service; Chairman, Subcommittee on Venereal Disease, National Research Council. 290 pages. Charles C Thomas, Springfield, Illinois. 1946.

cured of her own infection in her first pregnancy she should, according to Moore, be retreated in each subsequent pregnancy. The results of penicillin in pregnancy infections have compared very favorably with the results by arsenicals and the heavy metals. The abandonment of these latter therapies is recommended. A standard follow-up of infant and mother is suggested.

There is a short concluding chapter on streptomycin. On the basis of recorded observations, Moore states that streptomycin is unlikely to prove clinically useful in syphilis. The first half of this book is basic, and should be read by all who treat syphilis with penicillin. The last part of the book is a splendid exposition of present-day therapy with this antibiotic.

PHILIP F. WILLIAMS.

In this account of **Radical Surgery in Advanced Abdominal Cancer**[30] Dr. Brunschwig details the operative technique of many of the 100 such cases which form the subject of his report. The radical attack upon this seemingly hopeless and apparently inoperable group in an effort to afford them a certain degree of palliation produced a truly amazing salvage of 19 patients who survived the massive resections from two to ten years. It would appear from the favorable results obtained in many of these cases, Chapter Three, that too great consideration for medical contraindications should not prevent exploratory laparotomy for advanced abdominal cancer. The chapter on preparation of such cases for operation brings out the fullest application of the advances of recent research on shock, anesthesia, biochemistry, nutrition, and chemotherapy. As described in the chapter on supportive treatment, one can agree that the fullest use of such measures must modify the previous concepts of operability. The sections of the nutritive state in relation to protein metabolism and on parenteral nitrogenous nutrition discuss fully the expanding use and efficiency of such methods of nutrition.

The various, and usually multiple, operations for cancer arising in the stomach, small intestine, colon, pancreas, liver, and bile ducts, as well as a discussion of the treatment of injuries to vessels and operations on the spleen and adrenal glands, form the subject matter of fourteen chapters.

Probably the readers of this JOURNAL may be more interested in the author's remarks on the treatment of intra-abdominal extension of gynecologic cancer, than some of the preceding topics. Certainly a reading of these case reports makes one feel that such extensive resections often may be of value in the case regarded as hopeless. In a discussion of the complications following irradiation therapy, obstruction of the intestines or radiation ulcers, the author points out that many such cases should not at once be regarded as recurrent carcinoma. The evidence of 30 per cent palliation and 19 per cent prolonged survival indicates the need for a more radical attitude toward advanced abdominal cancer by those qualified to attempt such surgery.

PHILIP F. WILLIAMS.

This monograph **Heparin in the Treatment of Thrombosis** by J. Erik Jorpes,[31] who has done outstanding research on the subject, presents a detailed account of the chemistry and physiology of heparin, and the accumulated experience with this agent in the treatment of thrombosis. There are also extended sections on the nature and use of dicoumarol, as well as a discussion of the pathogenesis of thrombosis and its social aspects. Learmonth, in this foreword, in remarking on the prevalence of thrombo-embolic conditions in peacetime in all countries, states that in Sweden it is a particularly formidable problem. To those interested in any aspect of this anticoagulant, now regarded as specific in thrombosis as

[30] **Radical Surgery in Advanced Abdominal Cancer,** by Alexander Brunschwig, M.D., Professor of Surgery, University of Chicago. 318 pages. With 118 illustrations. The University of Chicago Press, Chicago, Illinois. 1947.

[31] **Heparin in the Treatment of Thrombosis,** An Account of Its Chemistry, Physiology, and Application in Medicine, by J. Erik Jorpes, M.D., Reader in biochemistry, The Caroline Institute, Stockholm, Sweden, with a foreword by J. R. Learmonth, C.B.E., Ch.M., F.R.C.S.E. Professor of Surgery, University of Edinburgh. Second Edition. 257 pages. Illustrated. Oxford University Press, London, New York, Toronto. 1946.

insulin in diabetes, the book offers a full and clear discussion of recent research and clinical experience.

The value of prophylactic postoperative treatment was demonstrated in a series of gynecologic cases at Stockholm. The material selected was known to give a high frequency of thrombosis. In 140 cases the dosage, 50 + 50 + 100 mg. daily as recommended by Crafoord, was given. There was one thrombosis. In approximately 100 other cases in the series the dosage was 50 + 50 + 50 mg. Two patients had thrombosis, both had sepsis, and one died of sepsis. In the maternity at Lund a serious uterine hemorrhage in an early postpartum treatment series caused the drug to be withheld until from twelve to twenty-four hours after delivery. In a series of cases, 50 + 50 + 100 mg. dosage, there were two cases of late thrombosis, nineteenth day post partum. The author regards a routine and sufficiently prolonged therapy with heparin as giving almost complete protection against thromboembolic complications after surgical operations and childbirth. The author feels the use of dicoumarol, which is fully discussed, has a markedly specific therapeutic effect in thrombosis. Surgery of thrombosis, therapeutic ligation, early ambulation, and many other aspects of the problem are discussed in this valuable book.

PHILIP F. WILLIAMS.

Chronic Disease and Psychological Invalidism,[32] A Psychosomatic Study, has been written by Jurgen Ruesch, with a collaborating staff, and appears from the Division of Psychiatry, University of California Medical School and the Langley Porter Clinic, San Francisco. The monograph deals particularly with the psychologic system, economic and cultural determinants during convalescence, and their influence upon speed and degree of recovery. Since neither psychological, anatomic, and pathologic factors are entirely useful in determining a complete state of recovery, the author group have used a psychosomatic approach in a group of 187 cases of delayed recovery.

These cases have been identified according to the general characteristics of the population, various indices of adjustment, life habits, and the histories of social relationships and measurement of their personalities and intelligence, in which the Minnesota "Multiphasic Personality Inventory" was found most suitable. There are sections on medical aspects, psychosomatic relations, situational conflicts, and character problems. In these discussions there is much to interest the gynecologist in regard to the "operation hungry" patient, multiple castration, frigidity, abortion, and loss of menstruation. The authors note the simultaneous occurrence of psychological problems and of disease in 73 per cent of their delayed recovery cases. Again, of interest to the gynecologist is the study of the psychologic conflicts present in many of their patients in the nature of forced separation, divorce, childbirth, and widowhood. Such changes in the intimate human environment at the onset of the disease in which recovery did not occur happened in 45 per cent of the cases. The chapter on psychological problems in general medicine merits reading by all physicians. The situation of the "perpetually referred" patient is analyzed.

The authors have discussed the prognosis in the delayed recovery type of case, and note how some may be selected for therapy. While individual therapy is regarded as of advantage to most such patients, it is felt that many of these individuals after short primary individual therapy could be more advantageously treated as a group. The intricate psychological background of many gynecologic problems, as Deutsch has pointed out, necessitates as thorough consideration and therapy as the surgical treatment which may seem to be indicated. Probably in many of these individuals a consultation with a psychiatrist may benefit the patient as effectively as surgery.

PHILIP F. WILLIAMS.

---

[32] **Chronic Disease and Psychological Invalidism, A Psychosomatic Study.** By Jurgen Ruesch, M.D., in collaboration with Robert E. Harris, Ph.D., Carole Christiansen, M.A., Susanne H. Heller, B.A., Martin B. Loeb, B.A., Sally Dewees, M.S., Annemarie Jacobson, M.D., with a foreword by Karl M. Bowman, M.D., from the Division of Psychiatry, University of California Medical School and the Langley Porter Clinic, San Francisco. 191 pages. Published with the Sponsorship of The American Society for Research in Psychosomatic Problems, New York, 1946.

Dr. Spies details his **Experiences With Folic Acid**[33] in the treatment of anemias. He has found that the anemias which respond are the macrocytic diseases—pernicious anemia of Addison's; sprue, both tropical and nontropical; and the nutritional macrocytic anemias including those of pregnancy and pellagra. Just how he got particularly interested in the triad of folic acid is somewhat involved and unclear. He states that in some liver extracts, folic acid was discarded early in the preparation and yet these extracts were active. Nevertheless Spies tried the folic acid. In order to have an ample material, patients in Cincinnati, in the Nutrition Clinic of Birmingham, Alabama, in hospital from Havana, and in the Institute for Tropical Diseases of Puerto Rico were treated.

A very detailed account of the history taking and the minute and extensive physical examination is given, including particularly neurological and blood tests. One of the main differences between the Addisonian pernicious anemia and nutritional macrocytic anemia is that in the latter there is present free gastric hydrochloric acid. The author states that the results obtained with synthetic folic acid are almost incredible. Two hundred eighteen cases were studied. The leucopenias due to arsenic, sulfa, and aminopyrine do not respond to this form of therapy. There appears to be little doubt that the active substance in liver extract is not folic acid but a much more powerful factor, as yet not purified. The therapy consists not only in the usual methods of rest, adequate nutrition, but in addition some 20 mg. of folic acid per day. The monograph is very detailed in its diagnostic and therapeutic description and proves very interesting and worth-while reading.

R. T. FRANK.

Minder has written a **Textbook of Urology**[34] while stranded in Zürich by the war. He had previously functioned as professor of urology and director of the Urological University Clinic in Budapest. The book is written in the form of 25 lectures designed particularly for students and practitioners. It does not make an appeal to the specialist. Like similar books from the same publishing firm, it is gotten out faultlessly. It has side indices to make reference easy. For a book of its kind, the number of illustrations is distinctly sparse (62) and many of them diagrammatically simplified. This is a very thorough, complete and up-to-date presentation, which, however, has little to offer to the American student who has so many textbooks at his disposal.

R. T. FRANK.

The standard **Atlas of Human Anatomy**[35] originally published by Carl Toldt and adapted by M. Eden Paul which first appeared in 1919 and which in its first and second editions has been republished nine times, is now again available in its tenth incarnation.

It almost is tautologous to describe this well-known textbook consisting mainly of some 1,500 clearly drawn anatomical figures, many in two or more colors, with captions underneath each figure. A vast amount of additional information is contained in the many page footnotes in small print, as well as in the three appendices in Vol. II (567 in number). English, American and International terminology appears in each figure. It is good to have this old and trusty councillor again available.

R. T. FRANK.

---

[33]**Experiences With Folic Acid.** By Tom D. Spies, M.D., Associate Professor of Medicine, University of Cincinnati School of Medicine; Director of the Nutrition Clinic, Hillman Hospital, Birmingham, Alabama. 110 pages. The Year Book Publishers, Inc., Chicago. 1947.

[34]**Lehrbuch Der Urologie** von Prof. Dr. Med. J. Minder, chem. Ordinarius für Urologie und Direktor der Urolog. Universitäts-Klinik Budapest zur Zeit Specialarzt der Urologie in Zürich. 348 pages. Hans Huber, Bern, Switzerland. 1946.

[35]**An Atlas of Human Anatomy.** For Students and Physicians. By Carl Toldt, M.D., assisted by Professor Alois Dalla Rosa, M.D. Adapted to English and American and International Terminology by M. Eden Paul, M.D., Brux., M.R.C.S., L.R.C.P. Volume I.—Second Edition Containing Sections on Regions of Human Body, Osteology, Arthrology, Myology (Figures 1 to 640, and General Index to the two Volumes). 390 pages. Volume II.—New Second Edition Containing Sections on Splanchnology, Angeiology, Neurology, Organs of the Senses (Figures 641 to 1505, with Appendices, and General Index to the two volumes). 452 pages. The Macmillan Company, New York. 1944.

The U. S. Pharmacopeia. The thirteenth edition of this monumental work has recently been issued by the authority of the U. S. Pharmacopeial Convention and is official from April 1, 1947.[36] First published in 1820, the history of its further progress constitutes an important chapter in American medical annals. The Pharmacopeia is a therapeutic guide to the profession, it presents a review of the progress in medicine and surgery progress from a critical and unbiased evaluation emanating from authoritative sources, and the preparations listed are prepared in accordance with accepted official standards of quality, purity, and strength. The inclusion of the various glandular products, vitamins, antibiotics, sulfa drugs, etc., constitutes valuable information for the gynecologist and obstetrician.

GEO. W. KOSMAK.

The continued and expanding teaching of sex education in schools and other institutions where young people are brought together necessitates an educational service for those who must do the teaching. This small volume, "**Sex Education, A Guide for Parents, Teachers, and Youth Leaders,**" by Cyril Bibby[37] gives ample material for those to whom such education is entrusted. The author discusses in early chapters the responsibility of such teaching, the receptive age, the amount and nature of the instruction in relation to the questions of childhood, and the growing interest in domestic biology in the school child. The psychology of adolescence and the teaching of normal reproductive biology to high school and college students are described.

For those in whose hands such instruction is placed, parents, teachers, physicians, nurses, there is much of practical value in the six appendices as to education methods from the toddler, asking where the new baby came from, to the young man and woman who seek information on marriage hygiene and family planning.

PHILIP F. WILLIAMS.

---

[36]**The Pharmacopeia of the U. S. of America.** Thirteenth Edition. Including supplements when issued. Easton, Pennsylvania, Mack Printing Company, 1947.

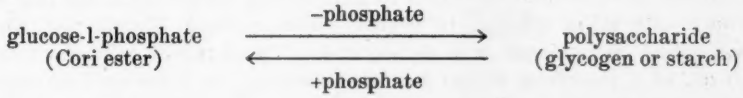
[37]**Sex Education: A Guide for Parents, Teachers and Youth Leaders.** By Cyril Bibby, M.A., M.Sc., F.L.S., Education Officer to the Central Council for Health Education. 311 pages. Emerson Books, Inc., New York. 1946.

Correspondence

Phosphorylase Activity in Human Endometrium

To the Editor:

It is now well known[1] that production of glycogen in the major glycogen depots (muscle, liver) is mediated by an enzyme phosphorylase which catalyzes a reversible equilibrium of the following general form:



Direct evidence has not hitherto been adduced, however, for the operation of this system in an important glycogen depot tissue of the female reproductive tract, the secretory uterine mucosa.

Abundant stores of glycogen are deposited in the gland cells of primate endometrium (human, macaque) during the progestational (secretory) phase of a normal menstrual cycle. It is found, however, that in a condition "glycopenia uteri," which is associated with sterility, the endometrium, although anatomically of the progestational type, is poor in glycogen as compared to the normal.[2, 3] The possibility arises that glycogen of secretory endometrium is designed to play a specific role in the maintenance of the life of the fertilized ovum. In view of this conjecture, and in consideration of the diagnostic importance of glycogen in the examination of the causes of infertility, information concerning the enzyme basis of glycogen production in human endometrium was felt to be desirable.

The specimens of endometrium were taken by curetting from 20- to 40-year-old women with diagnosis of uterine myoma or complaint of infertility, and who had reported normal menstrual cycles. The tissue was obtained in the operating room and sent to the laboratory in a dish over ice. A small sample was set aside for histologic analysis, and the remainder was used for the enzyme tests. The interval from curetting until analysis of enzyme activity was about fifteen minutes.

Phosphorylase activity was ascertained according to methods which have been described in connection with a survey of phosphorylase in rat tissues by Shapiro and Wertheimer.[4] Phosphate was determined according to Sumner[5] with a Pulfrich photometer set at filter S61.

In the presence of a strong amylase activity, the conversion of Cori ester into glycogen by an extract cannot be expected to lead to an actual accumulation of glycogen in the solution. Phosphorylase activity in such a case should nevertheless leave its mark in terms of: (a) a liberation of inorganic phosphate (P_0) in a medium containing Cori ester; (b) a decrease of inorganic phosphate (P_0) by interaction with glycogen in mixtures which contain a sufficient excess of the latter. A method based on (*a*) was employed to investigate the phosphorylase activity of endometrium in a group of four cases. A method based on (*b*) was employed in a series comprising a total of 16 cases.

1. *Effect of extract of endometrium on Cori ester.*—These experiments included tests on two secretory and two proliferative specimens. The technique was as follows: The fresh tissue was minced and extracted for thirty minutes in the cold with an equal weight of water. The filtrate was purified by adsorption on alumina gel and elution in a solution of glycerophosphate according to the procedure of Shapiro and Wertheimer.[4] A test mixture was made of 1 ml. purified extract (volume of eluate equivalent to 1 Gm. fresh tissue) and 0.5 ml. of a substrate mixture in which was containued 3 per cent Cori ester, 1.5 per cent glycogen, and

a trace of muscle adenylic acid in n/10 sulfuric acid. The final pH was 7.3. The mixture was incubated at 37° C. for one hour and then examined for P_o. Control tests were run on enzyme-blank and substrate-blank reaction mixtures.

Purified extract of a secretory endometrium, taken from a myoma patient in the twenty-second day of the cycle, failed to mediate hydrolysis of glycerophosphate, but liberated 0.14 mg. P_o from Cori ester in the conditions described. It may be concluded, therefore, that the extract contained some phosphorylase. A second examined secretory endometrium specimen behaved similarly.

On the other hand, extracts from two proliferative endometrium specimens failed to liberate P_o from Cori ester in the test conditions which have been described, and were therefore entirely lacking in any phosphorylase activity.

2. *Phosphorolysis of glycogen by homogenates of endometrium.*—Specimens of human endometrium were tested for phosphorolysis activity on glycogen as follows: the cooled tissue material, at arrival in the laboratory within roughly fifteen minutes from the time of curetting, was rinsed once with saline solution to remove adhering blood, blotted with filter paper to remove excess saline, and minced in a chilled dish. Two hundred milligrams of mince was added to 1.0 ml. of a phosphate Ringer mixture in which 1 or 5 per cent glycogen and m/40 sodium fluoride were included. The phosphate Ringer had the following composition: 4 ml. potassium chloride, 1.15 per cent; 1 ml. magnesium sulfate, 0.8 per cent; 100 ml. sodium chloride, 0.9 per cent; 60 ml. m/10 phosphate buffer of pH 7.4. Fluoride was included in the mixture to ensure that masking of phosphorolysis by secondary reactions of dephosphorylation would not occur. The suspension was shaken at 37° C. for two hours. Reaction was stopped with 0.5 ml. of 20 per cent trichloracetic acid. After addition of 5.0 ml. water, the suspension was filtered. P_o was determined promptly in an aliquot of the filtrate. The amount of P_o present at the beginning of the incubation period was determined in parallel control tests. The found decrease in P_o was expressed in per cent of P_o added at the outset.

Demonstration of phosphorolysis activity by this method proved to be dependent on the use of a sufficient excess of glycogen in the test mixture. When the glycogen level was low (1 per cent), several tested secretory specimens failed to mediate a measurable decrease of the phosphate level. When, however, the glycogen content of the test mixtures was increased to 5 per cent, homogenates prepared from the secretory type specimens caused uniformly, as may be seen in Table I, a definite decrease of inorganic phosphate ($-\Delta P_o = 11 - 18\%$). All tested proliferative type (six intermenstrual and three anovulatory cycle premenstrual) specimens, on the other hand, showed lower or even insignificant phosphorolysis activity in the same conditions ($-\Delta P_o = 0 - 9\%$).

The data which have been set forth indicate first that progestational human endometrium contains phosphorylase, and, second, that the phosphorolysis activity of endometrium as measured in a homogenate of the tissue rises markedly as the endometrium progresses from proliferation to secretion. It may be recalled that Hughes[6] has demonstrated the presence in human endometrium of an amylase system and has shown that this system, too, increases in activity during progestational growth.

The enzyme systems of endometrium which act on glycogen—phosphorylase and amylase—therefore vary cyclically in their activity in parallel to the glycogen content of the tissue. It is tempting to speculate on a casual relation between them. In this connection a sequence of the following form deserves consideration: phosphorylase → glycogen → amylase. The increase in phosphorylase activity during progestation is a self-evident cause of the increase in glycogen during this phase of the cycle. Of the increase of amylase activity during progestation, it can be supposed that it is in the nature of an adaptive or compensatory response to the glycogen rise.

The two different glycogen-oriented enzyme systems of endometrium do not duplicate the same function, but are mutually complementary. Phosphorylase in the endometrium is a synthesizing instrument. By its means the endometrium fixes diffusible sugar and retains it in the form of a nondiffusible and hence storable reserve stuff (glycogen). On the other

TABLE I. PHOSPHOROLYSIS OF GLYCOGEN BY ENDOMETRIUM TAKEN IN DIFFERENT STAGES OF THE MENSTRUAL CYCLE

CASE	DAY IN CYCLE	COMPLAINT	FOUND DECREASE OF INORGANIC PHOSPHATE IN PER CENT OF INITIAL VALUE
	I. *Secretory Premenstrual Specimens*		
1	18	Myoma	12
2	21	—	18
3	24	—	11
4	25	—	15
5	27	Sterility	14
6	27	Sterility	14
7	27	Sterility	16
	II. *Proliferative Intermenstrual Specimens*		
8	8	Myoma	9
9	9	Myoma	2
10	11	Myoma	5
11	11	Sterility	0
12	12	Myoma	1
13	16	Myoma	1
	III. *Proliferative Premenstrual (anovulatory cycle) Specimens*		
14	24	Sterility	4
15	25	Sterility	9
16	28	Sterility	5

hand, amylase can only serve in an opposite capacity. By means of amylase the tissue is able to mobilize its glycogen reserve and convert it into sugars (maltose, glucose) which can diffuse through the membrane of the cell. Amylase is thus important in endometrium probably because it enables this tissue to put its accumulated depot of carbohydrate at the disposal of the invading ovum.

The following summary may be presented:

1. Human endometrium contains phosphorylase.

2. A marked rise in the phosphorylase activity of endometrium accompanies progestation. This rise accounts for the deposition of glycogen in endometrium during its progestational phase.

3. A division of physiologic function between the two glycogen-oriented enzyme systems—phosphorylase and amylase—of endometrium, and a possible mutual connection between them in their increase during progestation are discussed.

BERNHARD ZONDEK, M.D.
SHLOMO HESTRIN, PH.D.

GYNECOLOGICAL-OBSTETRICAL DEPT.
ROTHSCHILD-HADASSAH UNIVERSITY HOSPITAL
HORMONE RESEARCH LABORATORY, HEBREW UNIVERSITY
JERUSALEM, PALESTINE
FEBRUARY 16, 1947.

References

1. Cori, C.: Endocrinology **26**: 285, 1940.
2. Zondek, B., and Stein, Z.: Endocrinology **27**: 395, 1940.
3. Zondek, B., and Shapiro, B.: AM. J. OBST. & GYNEC. **44**: 345, 1942.
4. Shapiro, B., and Wertheimer, E.: Biochem. J. **37**: 397, 1943.
5. Sumner, G.: Science **100**: 413, 1944.
6. Hughes, E.: AM. J. OBST. & GYNEC. **49**: 10, 1945.

Item

American Congress on Obstetrics and Gynecology

Three panel-type morning sessions on the following subjects have been arranged:

1. *Anesthesia and Analgesia,* Tuesday, September 9, Dr. Nicholas J. Eastman, Chairman, with the cooperation of Dr. J. P. Greenhill, Chicago; Dr. John Adriani, New Orleans; Dr. Stuart Cullen, Iowa City; and Dr. Arthur Baptisti, Hagerstown.

2. *Cancer,* Wednesday, September 10, Dr. Robert A. Kimbrough, Philadelphia, Chairman, with the cooperation of Dr. John Randall, Iowa City; Dr. Charles L. Martin, Dallas; Dr. Joe V. Meigs, Boston; and Dr. Herbert Schmitz, Chicago.

3. *Cesarean Section* on Thursday, September 11, Dr. Edward Schumann, Philadelphia, Chairman, with the cooperation of Dr. Edward G. Waters, Jersey City; Dr. Edward Davis, Chicago; Dr. E. D. Plass, Iowa City; and Dr. William Benbow Thompson, Hollywood.

The afternoon meetings of the Medical Section of the Congress will consider the Psychosomatic Aspects of Pregnancy on Tuesday; Pregnancy Complicated by Heart Disease, Diabetes, and Tuberculosis on Wednesday; and Recent Advances in Endocrinology on Thursday.

Round table discussions from 4:00 to 5:00 P.M. daily will consider such topics as abortions, asphyxia, fibroids, prolonged labor, infertility, early ambulation, uterine bleeding, nutrition in pregnancy, endometriosis, the Rh factor, erythroblastosis, geriatric gynecology, and other pathologic conditions relating to obstetrics and gynecology.

Concurrent round table sessions will be held for nurses, hospital administrators, and public health workers.

A scientific and educational exhibit under the direction of Dr. J. P. Pratt of Detroit and a comprehensive motion picture program under the guidance of Dr. John Parks of Washington are in process of development. Those wishing to make applications for space in these exhibits, especially for time on the cinema program, are urged to make early application. Necessary blanks may be obtained from the office of the Congress, 24 West Ohio Street, Chicago 10, Illinois. Better hurry!

On Friday, the last day of the Congress, the entire morning will be given over to the program of the National Federation of Obstetric-Gynecologic Societies. Dr. James S. Taylor of Altoona is arranging this session.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

American Gynecological Society. (1876) *President,* Emil Novak, Baltimore, Md. *Secretary,* Norman Miller, Ann Arbor, Mich. Annual meeting to be announced.

American Association of Obstetricians, Gynecologists and Abdominal Surgeons. (1888) *President,* A. D. Campbell, Montreal, Quebec. *Secretary,* James R. Bloss, 418-11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 4-6, 1947.

Central Association of Obstetricians and Gynecologists. (1929) *President,* Earl C. Sage, Omaha, Neb. *Secretary-Treasurer,* John I. Brewer, 104 South Michigan Ave., Chicago, Ill. Annual meeting Louisville, Ky., Oct. 23, 24, and 25, 1947.

South Atlantic Association of Obstetricians and Gynecologists. (1938) *President,* J. Randolph Perdue, Miami, Fla. *Secretary,* E. D. Colvin, 1259 Clifton Road, N.E., Atlanta, Ga. Annual meeting at Augusta, Ga., February 12 to 14, 1948.

A. M. A. Section on Obstetrics and Gynecology. *Chairman,* William F. Mengert, Dallas, Texas. *Secretary,* A. B. Hunt, Mayo Clinic, Rochester, Minn. Annual meeting June, 1947.

New York Obstetrical Society. (1863) *President,* Albert H. Aldridge. *Secretary,* R. G. Douglas, 530 East 70th St., New York City. Second Tuesday, from October to May, Yale Club.

Obstetrical Society of Philadelphia. (1868) *President,* John B. Montgomery. *Secretary,* James P. Lewis, 1930 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.

Chicago Gynecological Society. (1878) *President,* Ralph A. Reis. *Secretary,* Herbert E. Schmitz, 25 East Washington St., Chicago 2, Ill. Third Friday, from October to June, Hotel Knickerbocker.

Brooklyn Gynecological Society. (1890) *President,* Alexander E. Dunbar. *Secretary,* William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.

Baltimore Obstetrical and Gynecological Society. (1929) *President,* Lawrence Wharton. *Secretary-Treasurer,* John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.

Cincinnati Obstetrical Society. (1876) *President,* Carroll J. Fairo. *Secretary,* Joseph G. Crotty, 136 West McMillan St., Cincinnati, Ohio. Third Thursday of each month.

Louisville Obstetrical and Gynecological Society. *President,* Samuel S. Gordon. *Secretary,* J. B. Marshall, 605 Brown Bldg., Louisville, Ky. Meetings at the Brown Hotel every fourth Monday, from September to May, excluding December.

Portland Society of Obstetrics and Gynecology. *President,* Ronald Frazier. *Secretary-Treasurer,* Gifford D. Seitz, 919 Taylor St. Bldg., Portland 5, Ore. Meetings last Wednesday of each month.

Pittsburgh Obstetrical and Gynecological Society. (1934) *President,* Charles J. Barone. *Secretary,* Eugene A. Conti, 519 North Highland Ave., Pittsburgh 6, Pa. First Monday of October, December, February, April, and June.

Obstetrical Society of Boston. (1861) *President,* Frederick J. Lynch. *Secretary,* Paul A. Younge, 1101 Beacon Street, Brookline, Mass. Third Tuesday, October to April, Harvard Club.

New England Obstetrical and Gynecological Society. (1929) *President,* Arthur E. G. Edgelow, Springfield, Mass. *Recorder,* Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and December.

Pacific Coast Obstetrical and Gynecological Society. (1931) *President,* Henry N. Shaw. *Secretary-Treasurer,* William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif. Next meeting in Seattle, Wash., Oct. 1 to 4, 1947.

Washington Gynecological Society. (1933) *President,* Lawrence Lee Cockerille. *Secretary,* Raymond T. Holden, 3111 16 Street, N.W., Washington 10, D. C. Fourth Saturday, October, November, January, March, May.

New Orleans Obstetrical and Gynecological Society. (1924) *President,* Eugene H. Countiss. *Secretary,* Joseph W. Reddoch, Pere Marquette Bldg., New Orleans, La. Meetings held October, November, January, March, and May.

---

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

St. Louis Gynecological Society. (1924) *President,* Otto Krebs. *Secretary,* John E. Hobbs, 630 S. Kingshighway, St. Louis, Mo. Meetings second Thursday, October, December, February, and April.

San Francisco Gynecological Society. (1929) *President,* Albert M. Vollmer. *Secretary,* Daniel G. Morton, University of California Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.

Texas Association of Obstetricians and Gynecologists. (1930) *President,* T. F. Bunkley. *Secretary,* J. McIver, 714 Medical Arts Bldg., Dallas, Tex.

Michigan Society of Obstetricians and Gynecologists. (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President,* Clarence E. Toshach. *Secretary,* John P. Ottaway, 1551 Woodward Ave., Detroit, Mich. Meetings first Tuesday of each month from October to May (inclusive).

Central New York Association of Obstetricians and Gynecologists. (1938) *President,* Edward C. Hughes. *Secretary,* Nathan N. Cohen, 713 E. Genesse St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.

Alabama Association of Obstetricians and Gynecologists. *President,* Gilbert F. Douglas. *Secretary,* Hunter Brown, 1922 South Tenth Ave., Birmingham, Ala.

San Antonio Obstetric Society. *President,* I. T. Cutter. *Secretary,* S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.

Seattle Gynecological Society. (1941) *President,* Carl M. Helwig. *Secretary,* Roger E. Stewart, Stimson Bldg., Seattle, Wash. Meetings held on third Wednesday of each month.

Denver Obstetrical and Gynecological Society. (1942) *Secretary,* Emmett A. Mechler, 1612 Tremont St., Denver, Colo.

Wisconsin Society of Obstetrics and Gynecology. (1940) *President,* J. M. Freeman. *Secretary-Treasurer,* Lionel T. Servis, 425 East Wisconsin Ave., Milwaukee. Meetings held in May and October.

San Diego Gynecological Society. (1937) *President,* R. C. Hall. *Secretary,* D. Dalton Deeds, 2001 Fourth Ave., San Diego, Calif. Meetings held on the last Wednesday of each month.

North Dakota Society of Obstetrics and Gynecology. (1938) *President,* Ralph E. Leigh, Grand Forks. *Secretary,* G. Wilson Hunter, 807 Broadway, Fargo, N. D.

Virginia Obstetrical and Gynecological Society. (1936) *President,* S. E. Oglesby. *Secretary,* L. L. Shamburger, 628 State Office Bldg., Richmond 19, Va. Next meeting not announced.

Columbus Obstetrical and Gynecological Society. (1944) *President,* Wynne M. Silbernagel. *Secretary,* Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held fourth Wednesday of each month.

Naussau Obstetrical Society. (1944) *President,* Austin B. Johnson. *Secretary,* Robert S. Millen, Westbury, N. Y. Meetings, bimonthly from October to May.

Bronx Gynecological and Obstetrical Society. (1924) *President,* George Muscillo. *Secretary,* Milton D. Klein, 1882 Grand Concourse, New York 57, N. Y. Meetings, fourth Monday monthly from October to May.

Washington State Obstetrical Society. (1936) *President,* John H. Fiorino, Everett. *Secretary,* H. H. Skinner, Yakima, Meetings, first Saturday of April and October.

Kansas City Obstetrical and Gynecological Society. (1922) *President,* Thomas J. Sims. *Secretary,* LeRoy Goodman, 702 Bryant Bldg., Kansas City, Mo. Meetings, last Thursday, September, November, January, and March; first Thursday, May, University Club.

Los Angeles Obstetrical and Gynecological Society. (1914) *President,* George E. Judd. *Secretary,* Carl E. Krugmeier, 2200 West Third Street, Los Angeles, Calif.

North Carolina Obstetrical and Gynecological Society. (1932) *President,* Wallace B. Bradford. *Secretary,* Richard B. Dunn. Meetings semiannually.

The Society of Obstetricians and Gynecologists of Canada. (1944) *President,* William A. Scott. *Secretary,* James Goodwin, 516 Medical Arts Bldg., Toronto, 5. Meetings held annually, date of next meeting to be announced later.

Akron Obstetrical and Gynecological Society. (1946) *President,* L. L. Bottsford. *Secretary-Treasurer,* N. E. Wentsler, 1029 Second National Bldg., Akron 8, Ohio.

Minnesota Society of Obstetrics and Gynecology. *President,* L. M. Randall. *Secretary,* Russell J. Moe, 205 West Second St., Duluth, Minn. Meetings held spring and fall.

Miami Obstetrical and Gynecological Society. (1946) *President,* M. C. Wilson. *Secretary,* George A. Mitchell, Huntington Bldg. Meetings, second Thursday in January, March, May, and November.

Omaha Obstetrical and Gynecological Society. (1947) *President,* M. E. Grier. *Secretary,* B. V. Reaney, 1116 Medical Arts Bldg., Omaha 2, Neb. Meetings held third Wednesday in January, March, May, September, November.

Oklahoma City Obstetrical and Gynecological Society. (1940) *President,* Le Roy H. Sadler. *Secretary-Treasurer,* John W. Records, 301 Northwest 12 Street, Oklahoma City.

Cleveland Obstetrical and Gynecological Society. (1947) *President,* Robert E. Faulkner. *Secretary,* G. Keith Folger, 10515 Carnegie Ave. Meetings on fourth Tuesday of September, November, January, March, and May at University Club, 3813 Euclid Ave., Cleveland 15, Ohio.